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Full Name of Author — Nom complet de l'auteur
J. M. Robert Parker

Date of Birth — Date de naissance
12/Sept/1949

Country of Birth — Lieu de naissance
Canada

Permanent Address — Résidence fixe
4119-19 ave
Edmonton Alta
T6L 3C6

Title of Thesis — Titre de la thèse
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M. J. Robins

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THE UNIVERSITY OF ALBERTA

FURANOMYCIN RELATED C-GLYCOSYL AMINO ACIDS

BY

© JOSEPH MARK ROBERT PARKER

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
OF

DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA
SPRING 1980

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled

"FURANOMYCIN RELATED C-GLYCOSYL AMINO ACIDS"

submitted by JOSEPH MARK ROBERT PARKER in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

MJ Robins
Supervisor

Josef Takats

External Examiner

Feb 14th/80
Date

To

my father, Roland

my mother, Theresa

and

my wife, Helen

ABSTRACT

Several synthetic routes were investigated for the total synthesis of the antibiotic furanomycin. This natural product had been assigned the structure 2(*S*)-amino-2-[2,5-dihydro-5(*R*)-methylfuran-2(*R*)-yl]ethanoic acid. Early attempts in this thesis to form the desired β-C-glycosides which would be transformed to the cis-dihydrofuran glycine structure of the antibiotic involved alkylations of 5-*O*-trityl-2,3-*O*-isopropylidene-β-*D*-ribofuranosyl chloride and modified Strecker type syntheses with 2,5-anhydro-3,4,6-tri-*O*-benzoyl-*D*-allose and 2,5-anhydro-3,4-*O*-isopropylidene-*D*-allose. Several model reactions with methyl 2,3,5-tri-*O*-(methane and *p*-toluenesulfonyl)-β-*D*-ribofuranoside and 1,3-diphenyl-2-(2,3-*O*-isopropylidene-β-*D*-ribofuranosyl)imidazolidine were investigated to introduce the 5-deoxy and 2,3 unsaturated functions. The first approach which led to the formation of a *C*-glycosyl amino acid began with 1,3-diphenyl-2-(2,3,5-tri-*O*-benzyl-β-*D*-ribofuranosyl)imidazolidine. Hydrolysis of the N,N-diphenylethylenediamine protecting group gave an intermediate aldehyde which was treated directly with sodium cyanide and potassium carbonate followed by hydrogen peroxide. The resulting 3,6-anhydro-4,5,7-tri-*O*-benzyl-*D*-glycero-*D*-(allo and altro)-heptonamide was treated with methanesulfonyl chloride followed by displacement with lithium azide to give the corresponding α-azido amides. Acid hydrolysis followed by hydro-

genation over Pd-C gave 2-(R and S)-amino-2-(β-D-ribofuranosyl)ethanoic acid. In a continuing study to form the required C-glycosyl amino acid, the aldehyde generated by mild acid hydrolysis of 1,3-diphenyl-2-(2,3-di-O-benzyl-5-O-trityl-β-D-ribofuranosyl)imidazolidine was treated as previously described to give a mixture of 3,6-anhydro-4,5-di-O-benzyl-D-glycero-D-(allo and altro)-heptonamides. The amide and 2-hydroxy functions were protected as the N,O_2-isopropylidene derivative. Reaction of the free 7-hydroxy group with methanesulfonyl chloride followed by displacement with sodium iodide and reduction with hydrogen over Pd-C gave the desired 7-deoxy derivative. Simultaneous solvolysis of the isopropylidene and amide functions was affected with ANGC(H^+) resin in methanol. Mesylation of the free hydroxy group gave methyl 3,6-anhydro-4,5-di-O-benzyl-7-deoxy-2-O-methanesulfonyl-D-glycero-D-(allo and altro)-heptonoate. Debenzylation, followed by reaction with diimidazole thiocarbonate gave the 4,5-thiocarbonato derivative. Reductive elimination with trimethylphosphite (Corey-Winter procedure) gave methyl 3,6-anhydro-4,5,7-trideoxy-2-O-methanesulfonyl-D-(ribo and arabino)-hept-4-enoate. Attempts to displace the 2-O-mesyl function with azide were unsuccessful. In an alternate approach, acid hydrolysis of 1,3-diphenyl-2-(5-O-benzyl-2,3-O-isopropylidene-β-D-ribofuranosyl)imidazolidine gave the free aldehyde which was treated as before to give 3,6-anhydro-7-O-benzyl-4,5-O-isopropylidene-D-glycero-D-(allo and altro)-heptonamide.

After protection of the 2-hydroxy function with acetic anhydride, the 7-deoxy derivative was introduced by the following series of reactions, debenzylation followed by mesylation, displacement with sodium iodide and reduction of the iodo intermediate with hydrogen over Pd-C. Deprotection of the 2-acetyloxy derivative with methanolic ammonia followed by mesylation and displacement with lithium azide led to the formation of a key intermediate, 3,6-anhydro-2-azido-2,7-dideoxy-4,5-O-isopropylidene-D-glycero-D-(allo and altro)-heptonamide. Concomitant solvolysis of the amide and isopropylidene functions was achieved using ANGC(H$^+$) resin in methanol. The resulting α-azido ester was treated with diimidazole thiocarbonate to give the 4,5-O-thiocarbonato intermediate. Reductive elimination of the thiocarbonate function with trimethylphosphite gave accompanying reduction of the azide function.

Hydrolysis of this intermediate with 1N sodium hydroxide gave the desired products 2-(R and S)-amino-2-[2,5-dihydro-5(R)-methylfuran-2(R)-yl]ethanoic acid. This S-α-amino product, however, was not identical to the natural antibiotic. Further collaborative studies resulted in the assignment of furanomycin as 2-(S)-amino-2-[2,5-dihydro-5(S)-methylfuran-2-(R)-yl]ethanoic acid.

ACKNOWLEDGEMENTS

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INTRODUCTION

Microbes produce substances that can interfere with the normal function of other microorganisms. These inhibitory substances are called antibiotics. Antimetabolites, which include chemically synthesized substances, are inhibitors that interfere with mammalian and/or bacterial cell metabolism such as the inhibition of an enzyme (usually in a competitive fashion).[1-5] Competitive inhibitors are thought to combine with an enzyme at the same site as the natural substrate, compete with the latter and prevent the utilization of the normal substrate.

Antibiotics can disrupt metabolic pathways by several mechanisms:

(a) inhibition of cell wall synthesis (e.g. bacitracin, cephalosporin, penicillin, cycloserine, ristocetin, vancomycin)

(b) inibition of cell membrane function (e.g. amphotericin B, colistin, nystatin, polymyxin)

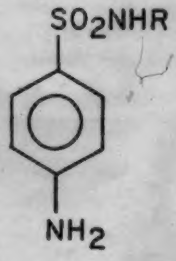
(c) inhibition of protein biosynthesis (e.g. puromycin, chloramphenicol, erythromycin, lincomycin, tetracyclin, amikacin, gentamicin, kanamycin, neomycin, streptomycin, tobramycin)

(d) inhibition of nucleic acid biosynthesis (e.g. nalidixic acid, novobiocin, pyrimethamine, sulfonamides, trimethoprim, rifampicin, actinomycin, mitomycin, halogenated pyrimidines).

Furanomycin, an antibiotic isolated from culture filtrates of Streptomyces L-803 was found to be a competitive inhibitor of L-isoleucine incorporation. The physical and spectral data obtained for the natural antibiotic by Katagiri and co-workers in 1967 and the chemical synthesis of racemic furanomycin achieved by Masamune and Ono in 1975, led these workers to assign the structure of furanomycin as 2(S)-amino-2-[2,5-dihydro-5(R)-methylfuran-2-(R)-yl] ethanoic acid. It was of interest to chemically synthesize this antibiotic from D-ribose since the stereochemistry had not been defined clearly.

A Brief History of Antimetabolites

The fundamental concept of antimetabolite activity was described by Ehrlich[6] as early as 1906, when he suggested that it should be possible to use substances toxic to infecting organisms but not to human cells. During the 1930-1940's studies by workers such as Foerster, Domagk and Woods [7,8] led to the observation that sulfonamides (1), which are structurally related



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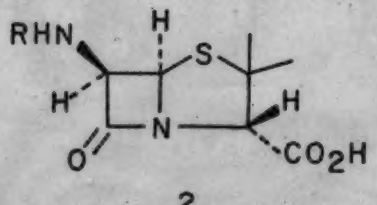
to p-aminobenzoic acid (a required vitamin for certain bacteria and other microorganisms in the synthesis of folic acid), effectively inhibited the growth of bacteria including streptococci and pneumococci.

The therapeutic use of penicillin (2) by Florey



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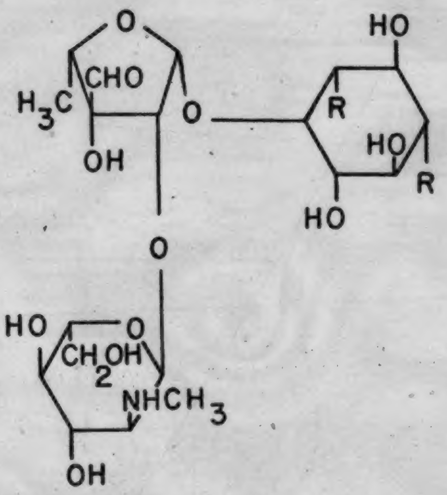
and Chain [9] in 1938, several years after its discovery by Fleming [10] in 1929, heralded what is described by many as the "Antibiotic Era". The term antibiotic, as defined today, was originally introduced by Waksman [11] in 1942.

Streptomycin (3) was first reported in 1944 [12] and

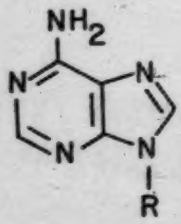


3 . R= $NH\overset{NH}{\overset{\|}{C}}-NH_2$

represents one of the first members of a new class of antibiotics called aminoglycosides. Even today, it remains as one of the preferred drugs in the treatment of tuberculosis. A detailed mode of action for streptomycin has been reviewed by Tanaka.[4] Dutcher [13] has classified the glycoside antibiotics into six subgroups: (1) those completely carbohydrate in nature, (2) those carbohydrates with unusual amino acids, (3) macrolide antibiotics, (4) pigmented glycosides, (5) nucleoside antibiotics and (6) polyenic amino sugars. The classification and chemistry of these glycosides has been the subject of several articles.[14,15]

Diverse classes of antibiotics were discovered, such as polymixin and chloramphenicol [16,17] in 1947, chlortetracycline [18] in 1948 and erythromycin [19] in 1952. The structural relationships, resistance mechanisms and biochemistry of these and other antibiotics have been discussed in detail.[20-25]

The study and identification of nucleoside antibiotics began with the isolation of cordycepin [26] (4) in 1951. Many examples of derivatives and analogues of adenosine (5) or cytidine (6) appear as nucleoside



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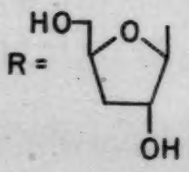

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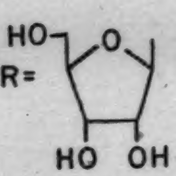

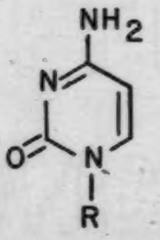

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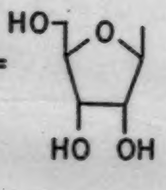
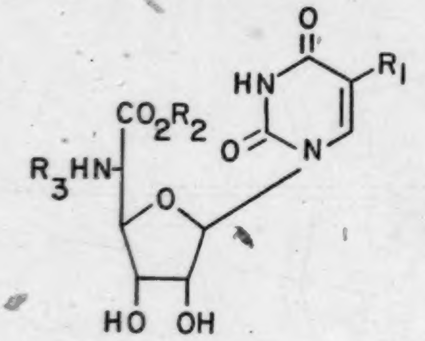


antibiotics.[27] Two main classes can be distinguished, the aminoacyl nucleosides which act as inhibitors of protein synthesis, and the adenosine analogues which act as antimetabolites of adenosine. Related to these nucleosides is the family of antibiotics known as the polyoxins (7). Of the twelve polyoxins initially isolated



R_1 = CH_2OH, CO_2H, CH_3

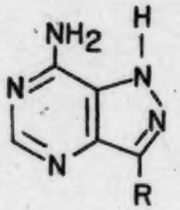
R_2 = 3-Ethylidene-L-azetidine-2-carboxylic acid

R_3 = 5-O-carbamoyl-2-amino-2-deoxy-L-xylonic acid or 3-deoxy derivative

7

and elucidated,[28-30] most are selectively toxic to fungi but have no inhibitory activity towards other organisms. The chemistry and biochemistry of the nucleoside antibiotics has been reviewed extensively.[25,27,28,31-33]

The identification of pseudouridine (8) in t-RNA [34,35] was followed by the isolation of several other C-nucleosides [28] which show antibiotic activity. The structures, chemistry and biochemical properties of these antibiotics such as formycin (9), oxazinomycin (10), pyrazomycin (11) and showdomycin (12) has stimulated considerable interest in new research on C-glycosides.



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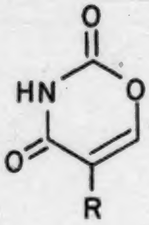

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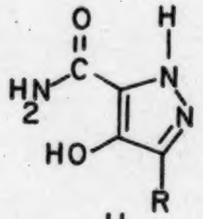

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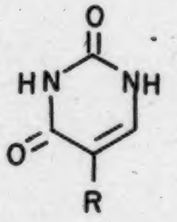

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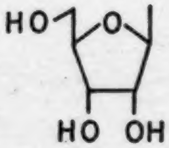

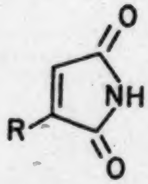

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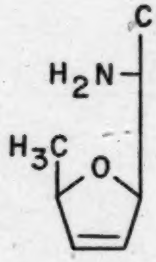
Furanomycin - Isolation and Structure

An antibiotic isolated from culture filtrates of Streptomyces L-803 was found to inhibit the growth of coliphage T2. The active principle, designated as furanomycin,[36] decolorized aqueous permanganate and bromine solutions, showed an absorption maximum at 196 nm and readily absorbed one mole of hydrogen. These facts indicate the presence of a double bond. Furanomycin as well as the dihydro derivative gave a positive ninhydrin test. This, together with the observation that the circular dichroism spectra show positive Cotton effects for both compounds suggests that furanomycin is an *L*-α-amino acid. The PMR spectra of furanomycin displayed a doublet at δ 1.33 (*J* = 6.4 Hz, 3) for a secondary methyl group, a doublet at δ 3.82 (*J* = 2.6 Hz, 1) for a proton of an α-amino acid, a quintet at δ 5.19 (1H), a multiplet at δ 5.42 (1H) and an AB quartet at δ 5.83 and 6.16 (*J* = 6.3 Hz, 2H) characteristic for double bond protons. This data is consistent with the proposed structure for furanomycin (*13*) or its diastereomer (*14*). By means of chemical degradation,



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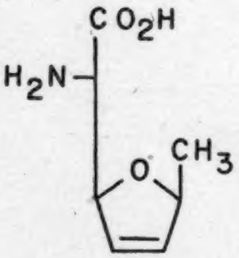

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furanomycin was converted to 2-hydroxymethyl-5-methyltetrahydrofuran. This compound was chemically synthesized and proved identical to that derived from furanomycin. This confirmed the basic carbon skeleton. Proton spin decoupling experiments on *13* indicated a large coupling constant (J_{3-6} = 5.7 Hz) between H_3 and H_6 which is consistent with *cis* substitution on the 2,5-dihydrofuran ring. It was concluded that furanomycin was 2(*S*)-amino-2-[2,5-dihydro-5(*R*)-methylfuran-

2(R)-yl]ethanoic acid (13) or its diastereomer (14).

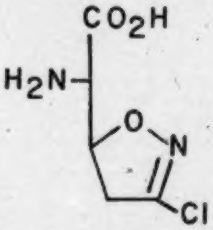
Biological Activity

Furanomycin inhibits the growth of several microorganisms. The inhibition of growth of Escherichia coli H by furanomycin (0.5 - 2 μM) was found to be reversed by isoleucine, valine and to a lesser extent, leucine. All other amino acids tested for reversal exhibited no effect. The ratio of concentration of furanomycin to isoleucine (0.1 - 10 μM) for complete inhibition of growth was approximately ten. Valine (0.2 - 0.5 μM) was as effective as isoleucine in reversing the inhibition at low concentrations but was ineffective at higher concentrations. Thus, it is thought that the mechanism of reversal is different for the two amino acids. The studies indicated that furanomycin is a competitive inhibitor of L-isoleucine utilization.

Currently there are several known antagonists of isoleucine. These include leucine,[37,38] methallylglycine,[39,40] ω-dehydroisoleucine,[41] 2-(R,S)-amino-2-(cyclohexene-4-(R,S)-yl)ethanoic acid,[42] 2-(R,S)-amino-2-(cyclopentene-3(R,S)-yl)ethanoic acid,[43] cyclopentaneglycine,[44] O-methylthreonine [45] and β-hydroxyleucine.[46] It has been suggested [36] that because of the structural similarity of furanomycin to cyclopentane glycine one might postulate a similar mode of action. Cyclopentane glycine had been determined to prevent the growth of Escherichia coli at concentrations of 20 - 30 μg per 10 ml. Of the common amino acids utilized in protein biosynthesis, only isoleucine, leucine, valine and threonine reverse the toxicity of cyclopentane glycine. A ratio of inhibitor to isoleucine of approximately thirty was required to produce complete inhibition with concentrations of isoleucine varying from 3 - 300 μg per 10 ml. At higher concentrations of isoleucine (300 - 3000 μg per 10 ml) this ratio dropped to ten. The effect of leucine or valine on reversing the inhibition by cyclopentane glycine is decreased in the presence of isoleucine. The results with valine and leucine may be related to the suggestion that these substances furnish some limiting precursor for the biosynthesis of isoleucine. It is also possible that at higher concentrations, valine and leucine may displace the inhibitor and substitute for isoleucine in some particular function. The reversal of cyclopentane glycine inhibition by α-keto-β-methylvaleric acid, the keto analogue of isoleucine, was also studied. It was suggested that the keto-acid was a precursor for isoleucine and also performed some other function essential to isoleucine metabolism.

It is interesting to note that an antitumor antibiotic closely resembling furanomycin was isolated from

Streptomyces suiceus.[47-49] The active substance, 2(S)-amino-2-[3-chloro-4,5-dihydro-isoxazol-5(S)-yl]ethanoic acid (15) was found to be a powerful inhibitor of mammal-



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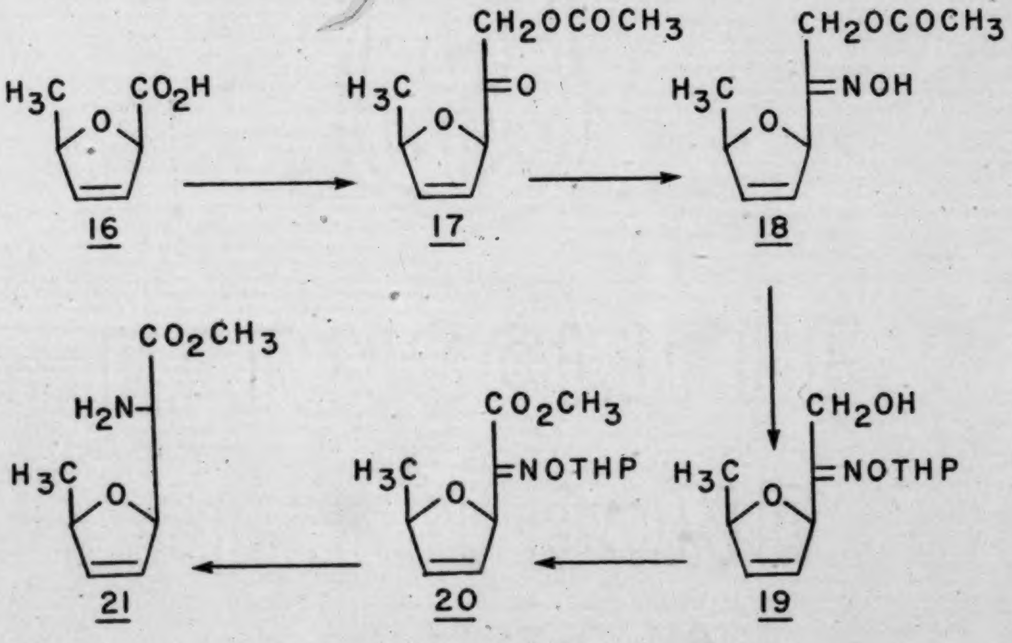
ian and bacterial reactions involving transfer of nitrogen from L-glutamine. This inhibitor prevented the utilization of L-glutamine by L-asparagine synthetase in mouse pancreas and tumor tissue in vivo and in vitro. The results from the in vitro studies indicated the inhibition to be competitive in nature.

A family of antifungal antibiotics, the polyoxins[30] (7) produced by Streptomyces cacaoi var. asoensis also appears to be related to the structure of furanomycin in some respects. The biological activity of the polyoxins is unique in that they are specifically inhibitory to phytopathogenic fungi but lack activity against gram positive and gram negative bacteria. Studies indicated that uptake of glucosamine was inhibited by the polyoxins. This suggested that the site of action may be related to cell wall chitin synthesis since glucosamine must be converted to uridine diphosphate-N-acetyl-glucosamine (UDPGlcNAc) before incorporation into chitin. It was suggested that polyoxin D and L may indeed be structural analogues of UDPGlcNAc. The kinetics of inhibition have been shown to be competitive and the blockage is reversed extensively by dipeptides such as glycyl-D,L-valine and D,L-alanylglycine.

Synthesis

Masamune and Ono[50] reported the synthesis of racemic furanomycin in 1975 as shown in Scheme I. By


CO_2H
H_3C
O
16
CH_2OCOCH_3
=O
17
CH_2OCOCH_3
=NOH
18
CH_2OH
=NOTHP
19
CO_2CH_3
=NOTHP
20
CO_2CH_3
H_2N
21

SCHEME 1

means of a limited Birch reduction on 5-methylfuroic acid, they isolated *cis*-5-methyl-2,5-dihydrofuroic acid (16) in approximately 40% yield. The acid 16 was converted to the acid chloride which was treated with diazomethane and acetic acid to give the keto acetate (17). The derived oxime 18 was obtained in overall yield of 47% from 16. The oxime acetate (18) was blocked with dihydropyran and treated with potassium carbonate to give the alcohol (19). This alcohol was oxidized to the acid and treated with diazomethane to give the methyl ester (20) in 77% yield. The tetrahydropyranyl ether was deprotected with acid and reduced with aluminum amalgam to give the α-amino ester (21), (8%) after chromatography, identical to that derived from furanomycin. The hydrochloride of this α-amino ester was hydrolysed in base and purified by paper chromatography to give D,L-furanomycin (69%), identical to an authentic sample by paper chromatography, TLC and PMR spectroscopy.

The absolute configuration still remains unknown because their product was a racemic mixture of D and L furanomycin. A stereo-defined synthesis of furanomycin from D-ribose would determine the absolute configuration without question. Such a project would involve aspects of both C-glycoside and α-amino acid synthesis.

Survey of C-glycosides

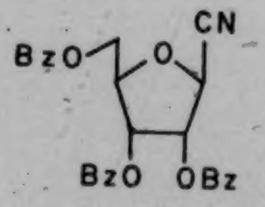
As early as 1850, C-glycosyl compounds were isolated from plant sources. No definitive work on structure determination appeared until the 1950's when

Muhlemann [51] proved the structure of Barbaloin to be a C-D-glucosyl derivative of 1,8-dihydroxy-3-(hydroxymethyl)anthrone. Haynes [52,53] has reviewed the early history of isolation and structure determination of C-carbohydrate derivatives reported prior to 1965 such as Anthrocene, Bergevin, Mangliferin and C-glucosylflavones.

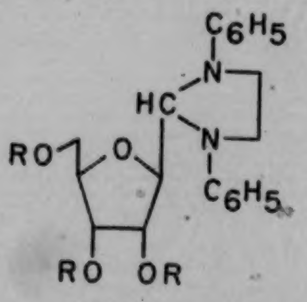
Recently, C-nucleosides isolated from natural sources have received much attention because of their similarity to normal cell metabolites. Many of these nucleoside analogues show antiviral and antibacterial activity and can be employed as important tools in metabolism studies. Stimulated by these results many new methods for C-glycoside synthesis have recently been developed. Reviews by Hanessian and Pernet [54a] as well as Daves and Cheng [54b] outline and evaluate current procedures in this area. Although several indirect routes are described, there are four general methods that prove to be synthetically useful:

1. β-D-ribofuranosyl Cyanide

One of the more widely used starting materials directly incorporating a β-C-glycosyl functionality is 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl cyanide (22) developed by Bobek and Farkas.[55] Functionalization of the nitrile was achieved by Moffatt and co-workers [56] by



22

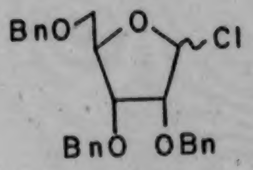


23 R = Bz, Bn

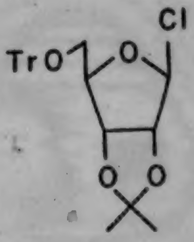
reduction to the imine and spontaneous hydrolysis to the aldehyde which was isolated as its N,N-diphenylethylenediamine derivative 23. The free aldehyde, generated by mild acid hydrolysis, proved to be quite versatile in the synthesis of many C-nucleosides. This was accomplished by reaction of the aldehyde with sodium cyanide and hydrogen peroxide to give an α-hydroxylamide derivative,[57] by reaction of the aldehyde with Wittig reagents[58] or by elaboration of its oxime derivative.[59]

2. Condensation with Carbanions

Because of the known problems with 1,2-*O*-ketal formation [60] encountered in reactions of glycosyl halides with carbanions when a C-2 participating group is present, sugars used in these condensations required benzyl or isopropylidene protecting groups. Tri-*O*-benzyl [61] (24) as well as 5-*O*-trityl-2,3-*O*-isopropylidene-β-*D*-ribofuranosyl chloride [62] (25) have been condensed with sodiodiethyl malonate and its derivatives.



24



25

It is interesting that this reaction with 25 gives predominantly the α anomer, implying it is the thermodynamically more stable product[62-65] under the reversible reaction conditions. Tri-O-benzyl ribose has also been reacted with Grignard reagents to give alkylated products at C-1.[66]

3. Wittig Reactions

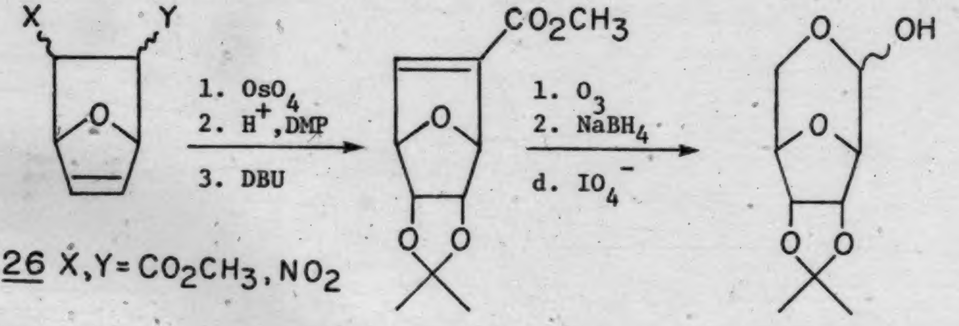
The most versatile route to C-glycosyl ethanoic acid derivatives was achieved by reacting 2,3-O-isopropylidene ribose derivatives and 2,3,5-tri-O-benzoyl ribose with substituted methylene phosphoranes.[67] This results in predominate if not exclusive formation of the β-anomer.

4. Condensations Employing Lewis Acid Catalysts

In the first reported synthesis of showdomycin, Sorm and co-workers[68] coupled sugar halides with 1,2,5-trimethoxybenzene using zinc oxide as catalyst. The coupled product was ozonolyzed to give an α-keto ester followed by a Wittig reaction and ring closure to the nucleoside. Several aromatic C-glycosides have been prepared by Kalvoda[69] and Ohrui[70] using Lewis acid catalyzed couplings. Condensation of 1-O-acetyl ribose derivatives with silyl enol ethers and silyl ketone acetals catalyzed by stannic chloride produced C-glycosyl compounds.[71] It is noteworthy that mixtures of anomers were obtained under these acidic conditions.

More recently, diverse methods have been employed to synthesize C-glycosyl compounds. Attempts to prepare 2,5-anhydro-D-allose derivatives by diazotization of α-amino-2-deoxy pyranosides have been studied.[72] Isopropylidene ribose and nitromethane have been condensed to give α and β-ribofuranosyl nitromethanes in low yield.[73] In the preparation of several C-nucleoside analogues, β-D-ribofuranosyl ethynes,[74] propiolates[75] and 3-cyano-2-propenoic acids have been described.[76] Chain extension and chain branching reactions in carbohydrates by Grignard reagents, Wittig reagents, base catalyzed aldol condensations and displacement with carbon nucleophiles, have been reviewed in detail.[77-79]

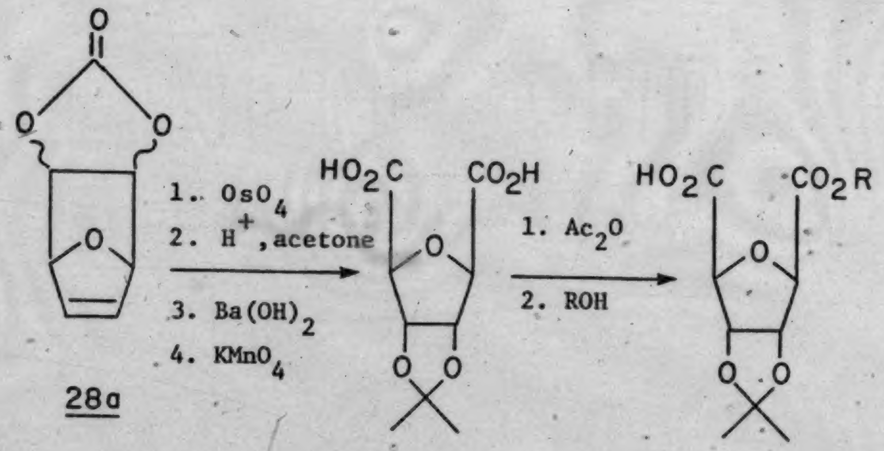
Several novel approaches have recently been developed in an attempt to form C-glycosides from non-carbohydrate precursors. As early as 1973, Just and co-workers[80,81] reported work on the Diels-Alder addition of methyl-β-nitro acrylate with furan. Chemical modification of the adduct 26 eventually gave racemic


X
Y
O
1. OsO_4
2. H^+,DMP
3. DBU
CO_2CH_3
O
O O
1. O_3
2. $NaBH_4$
d. IO_4^-
O
OH
O
O O

26 X,Y = CO_2CH_3, NO_2

27

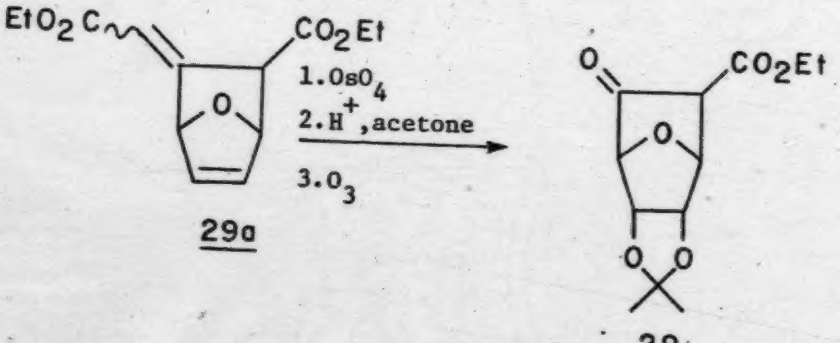
2,5-anhydroallose (27). A similar series of reactions beginning with cyclopentadiene gave the carbocyclic analogues. These derivatives were employed in the formation of several racemic C-nucleosides.[82-90] Schmidt and Lieberknecht[91] have developed an elegant chiral synthesis of D and L ribose derivatives 28 starting with 28a, the Diels-Alder adduct of vinylene carbonate


O
O
O
O
1. OsO_4
2. H^+,acetone
3. $Ba(OH)_2$
4. $KMnO_4$
HO_2C
CO_2H
O
O O
1. Ac_2O
2. ROH
HO_2C
CO_2R
O
O O

28a

28

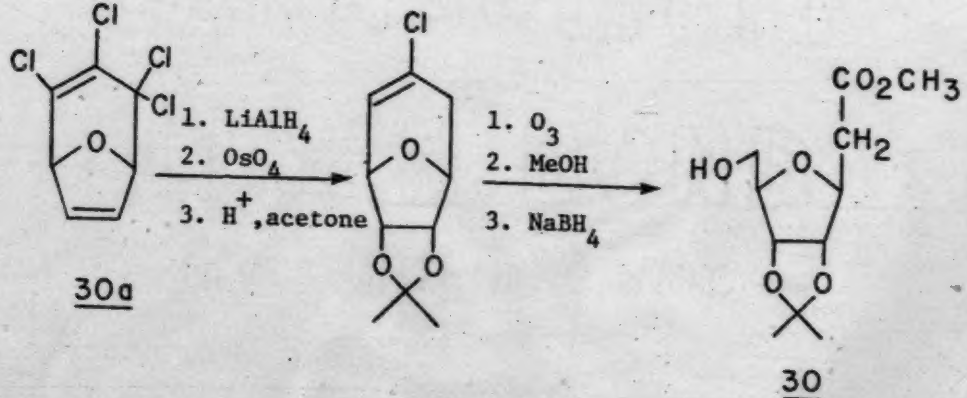
and furan. In a similar series of reactions other workers have treated 1,3-diethoxycarbonyl allene[92] with furan to give a racemic product (29a) that was further modified to give the key intermediate 29 in their synthetic scheme. Tetrachlorocyclopropane was reported[93]


EtO2C
CO2Et
O
1.OsO4
2.H+,acetone
3.O3
O
CO2Et
O
O O

29a

29

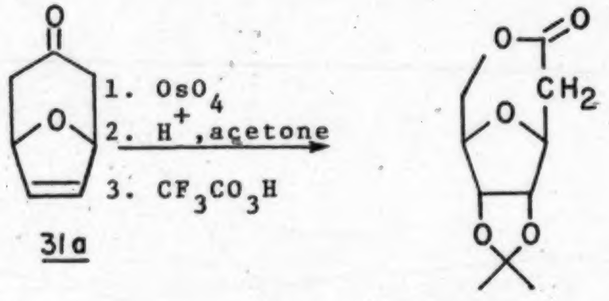
to react with furan to give an intermediate (30a) which was chemically transformed to a mixture of D and L-ribofuranosyl acetic acid derivatives (30). As part of a


Cl
Cl
Cl
Cl
O
1. LiAlH4
2. OsO4
3. H+,acetone
Cl
O
O O
1. O3
2. MeOH
3. NaBH4
CO2CH3
CH2
HO
O
O O

30a

30

study in C-glycoside synthesis, the reaction of α,α,α',α'-tetrabromoacetone and furan catalyzed by iron carbonyl gave 31a.[94-97] An optically resolved intermediate 31 was used to synthesize the C-



31a

31

nucleosides pseudouridine, pseudocytidine and 5'-modified derivatives.[95-97]

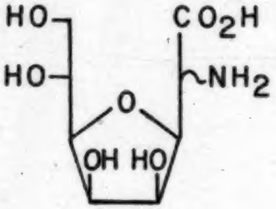
Survey of α-Amino Acid Syntheses

Because furanomycin can be considered as a C-alkylated derivative of glycine, a route could be devised to the title compound by elaboration of a preformed α-amino acid or its precursor.

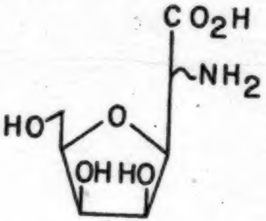
There are several well established synthetic routes[98-100] to α-amino acids among which are the Strecker synthesis and its modifications, amination of α-halo acids, Curtius rearrangement of azido acids and reduction of α-oximino esters. Alkylation of substituted acetamido,[101] α-formamido,[102] α-phthalimido,[103] and nitro[104] malonates also provides a versatile route to α-amino acids. The condensation of active methylene compounds with nitriles and aldehydes,[105-107] in particular the Erlenmeyer azalactone synthesis, has been extensively employed.

More recently, several methods to alkylate protected amino acids have been developed. Such procedures include Schiff bases,[108-111] silylated amino acids,[112] N,N-dimethylaminomethylene protected amino acids,[113] N-benzoyl glycine,[114] α-isocyanoesters,[115] ethyl nitroacetate [116] and 1-(chiral substituted)-2-imadazolin-5-ones.[117] Various other methods used to synthesize several amino acids include the reductive amination of α-keto esters with sodium cyanoborohydride and ammonia,[118,119] oxidation of amines with ruthenium tetroxide,[120] amidoalkylation of olefins,[121] Grignard reactions on ethyl N-trichloroethyl carbamate,[122] modified Strecker synthesis,[123] and nucleophilic displacement on 2-acetoxy-2-amino acid derivatives.[124]

A subject more closely related to this thesis is that of α-amino acids substituted by carbohydrate derivatives. Several of the earlier studies involved the C-4 derivatized sugar component of polyoxin,[125-128] the synthesis of deoxypolyoxin C and thymine polyoxin C,[129] 1-(5-amino-5-deoxy-β-D-allofuranosyl uronic acid)-uracil,[130] and C-3 [131,132] as well as C-2 [133] linked analogues of polyoxin. C-glycosyl amino acids linked to C-1 of a carbohydrate have been prepared by reaction of ethyl isocyanoacetate with D-manno-1,4-lactones. This gave β-D-mannofuranosyl glycine (32) which was further converted into β-D-lyxofuranosyl glycine (33).[134-136]

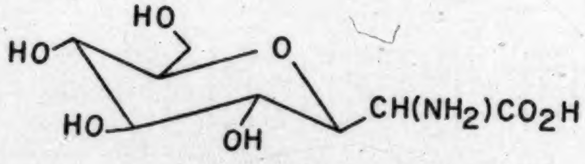

HO
HO
CO2H
NH2
O
OH HO

32

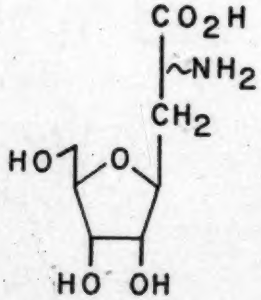

CO2H
NH2
HO
O
OH HO

33

Similar reactions with ethylcyanoacetate have been reported on ketoses and aldoses.[137] The reaction of 2-phenyloxazolin-5-one with α-acetobromoglucose or D-allose derivatives was reported to give (R,S)-α,β-D-glucopyranosyl glycine [138] (34) with the former and 3-(β-D-ribofuranosyl)-D,L-alanine [139] (35) with the latter.

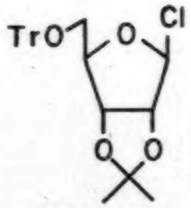

HO
HO
O
HO
OH
CH(NH2)CO2H

34

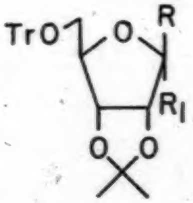

CO2H
NH2
CH2
HO
O
HO OH

35

RESULTS AND DISCUSSION



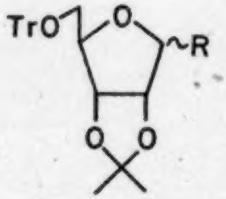
36



37 R= H R_1= $CH(CO_2Et)_2$
38 R_1=H R= $CH(CO_2Et)_2$

Our early attempts to form the desired β-C glycosides involved the alkylation of a ribofuranosyl chloride derivative as described by Fox and co-workers.[62] As reported, the reaction of the chloro sugar [140] (36) in dimethoxyethane with diethyl malonate and sodium hydride gave a mixture of α and β isomers 37 and 38. The reaction appeared to be quantitative as judged by TLC (toluene-ether (10:1), starting material R_f = 0.7, product R_f = 0.55 and 0.45). The ratio of the more polar isomer to the less polar isomer was estimated by TLC to favor the former (2:1) after a reaction time of one hour. Prolonged heating (12-17 h) changed this ratio in favor of the less polar isomer (1:4). Originally it was assumed that the more thermodynamically stable, less polar isomer, was the desired β isomer. This assumption was based on the anticipated steric interference between the isopropylidene and diethyl malonate groups. However, reinvestigation of this reaction by Moffatt and co-workers [63] produced evidence to the contrary. It had been established that the C_5 signals in the ^{13}C NMR spectra of pentofuranose derivatives occur at higher field for a cis relationship between C_5 and the hydroxyl group of C_3 than the trans configuration. The same appears to hold true for C_1 when there is a cis configuration between C_2OH and the aglycon. From the ^{13}C NMR spectral data obtained for 37 and 38, it was concluded that since the chemical shifts for C_2, C_3 and C_4 of the thermodynamically more stable isomer were upfield from those assigned for the kinetic product, the α-isomer was the more stable and predominate product.

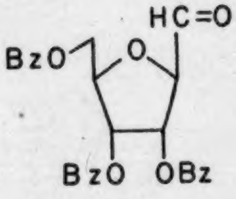
Attempts to further transform the product by decarboxylation using NaCN/DMSO, LiI/α-collidine and KOH/ETOH only led to decomposition. Problems involved with these basic hydrolysis conditions were probably compounded by anion formation at the diethyl malonate function. For this reason monosubstituted malonates were then investigated. It was hoped that the kinetic or β isomer would predominate since epimerization would not be possible once the product was formed. Using similar conditions to those described for diethyl malonate, both of the products with diethyl nitromalonate [141] (39) and diethyl acetamidomalonate [142] (40) appeared by TLC to give good yields of a mixture of α and β



39 R= $CNO_2(CO_2Et)_2$
40 R= $CNHAc(CO_2Et)_2$

isomers (toluene-ether (20:1), starting material R_f = 0.75, product R_f = 0.3 and 0.2). As shown by TLC, the more polar isomer predominated (4:1). If the analogy can be drawn to the reaction with diethyl malonate, this more polar isomer would be the desired β isomer. However, no definitive structural proof was completed. Chromatography of these malonate sugars led to decomposition in varying degrees. This was probably due to the acid lability of the protecting groups. Neutralization of the silica gel with saturated methanolic ammonia followed by drying of the silica under vacuum appeared to reduce the amount of material lost during chromatography. With this pretreated silica, 39 and 40 were obtained in yields of approximately 45-50%. Since these preliminary experiments did not give the β isomer exclusively and the isolation procedures gave unsatisfactory yields, this approach was not investigated further.

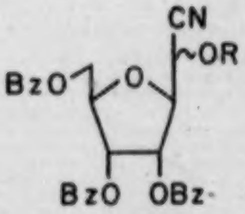
A seemingly more viable route involved starting with the imidazolidine (23, R = Bz) incorporating a preformed β C-glycoside linkage. Following the procedure described by Moffatt,[56] treatment of this imidazoline with three equivalents of p-toluene-sulfonic acid monohydrate gave the free aldehyde (41)which was



41

used without further purification. This aldehyde proved to be relatively stable in subsequent reactions if used immediately. If it was allowed to stand at room temperature extensive decomposition occurred. After generating the aldehyde intermediate care must also be taken to neutralize the excess acid with solid sodium bicarbonate. If most of the acid was not removed in this manner, decomposition resulted when the aldehyde solution was concentrated. Several modified Strecker type syntheses were investigated with the aldehyde. Reaction of 41 with sodium cyanide and benzylamine[143,144] gave a single product. However, the proton NMR spectrum revealed that no benzyl groups were present. Mass spectrometry was not consistent with the expected α-benzylamino nitrile derivative. As will be shown later, this product was actually the α-hydroxy nitrile derivative. Similar reactions of 41 with sodium cyanide, potassium carbonate and hydrogen peroxide,[56] or sodium cyanide and ammonium carbonate [145] resulted in hydrolysis of the benzoate groups under the basic reaction conditions.

Natta and Pasquon [146] described the synthesis of several α-amino acids from oximes using sodium metabisulfite and sodium cyanide. Similar treatment of the oxime derivative of 41 (described by Moffatt [59]) gave none of the desired α-aminonitrile. The product that was isolated appeared to be the α-hydroxy nitrile (42)

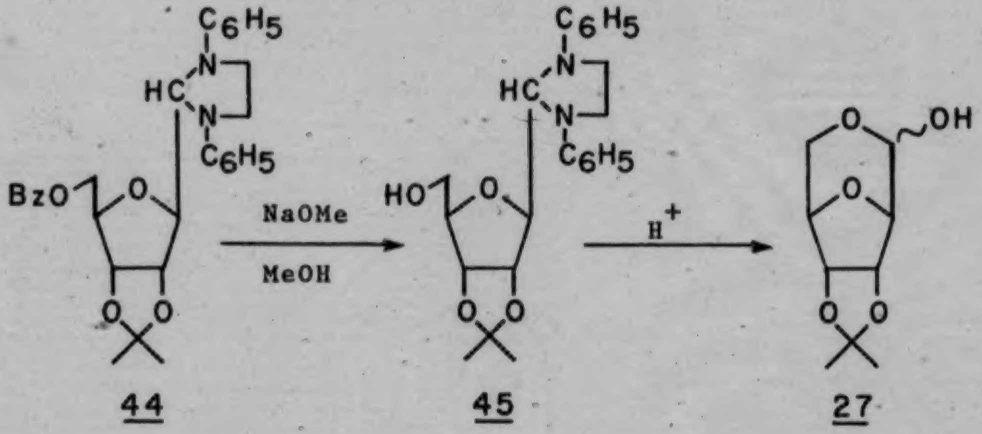


42 R=H

43 R= Ac

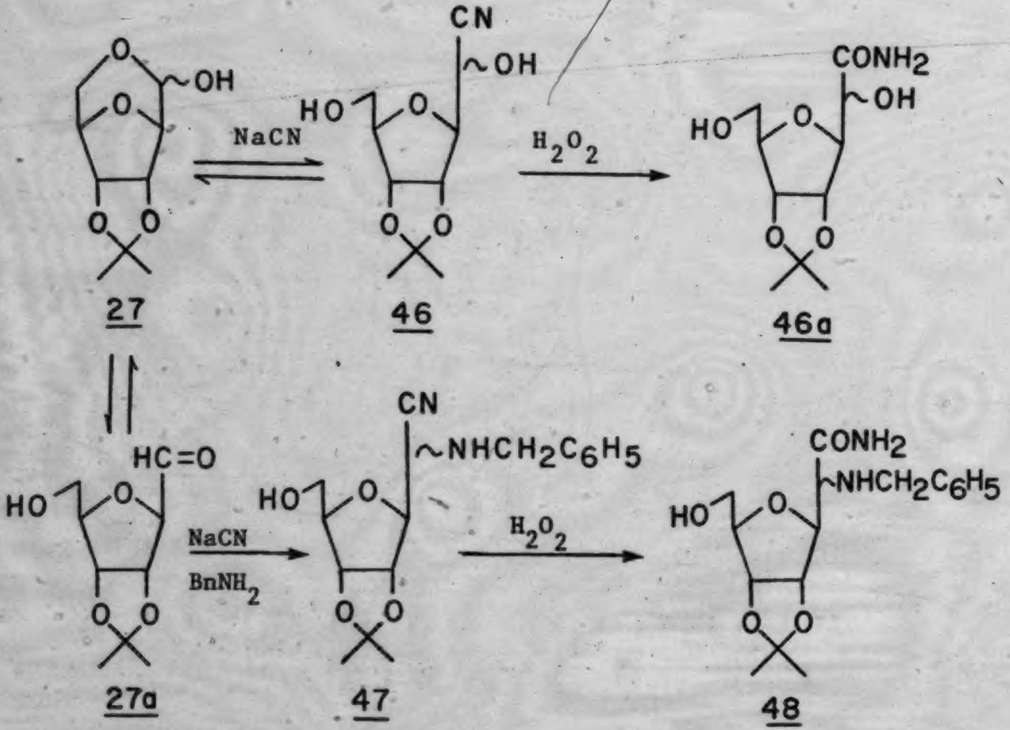
as deduced from the elemental analysis, PMR and IR spectra. Both the proton NMR and IR spectra indicated the presence of hydroxyl and benzoyl groups. The IR spectrum showed no absorption for a nitrile function . This is not unusual since it is known that electron withdrawing substituents adjacent to the nitrile reduce the intensity of the nitrile band normally found at 2240-2260 cm^{-1}. Unexpectedly, it was then observed that 42 formed readily in 91% yield upon treatment of 41 with sodium cyanide. Although this material (42) was stable if kept as a syrup at 0°C, attempted chromatography resulted in isolation of only a partially purified product. This result was contrary to that reported for the tribenzyl analogue.[56] In that case, the cyanohydrin product could not be isolated since it readily reverted to the aldehyde. Further proof for the proposed structure (42) was obtained from examination of its acetyl derivative (43) prepared in 76% yield using acetic anhydride in pyridine. It was found that the data obtained from elemental analysis, ^{1}H NMR and IR spectra were consistent with structure (43). The PMR spectrum information clearly indicated the presence of an acetyl function as a sharp singlet for three protons at δ 2.0. The IR spectrum had two bands in the ester region, one for the benzoyl group (1725 cm^{-1}) and a second for the acetyl group (1760 cm^{-1}). Attempts to hydrolyse the nitrile function of 42 with hydrobromic or hydrochloric acid in ethanol were unsuccessful. Since it appeared that these routes were not productive in yielding α-amino acid derivatives, other approaches were investigated.

It was considered that a modified Strecker synthesis on a 2,5-anhydro allose derivative would lead to the desired β C-glycosyl-amino acid. Such an intermediate (27) had been prepared in a multistep synthesis by Just and co-workers [80,81] as described previously in the introduction. Their product however, was a mixture of D and L -allose derivatives. In this laboratory 2,5-anhydro-3,4-O-isopropylidene-D-allose was prepared as shown in Scheme II. Hydrolysis of the



SCHEME II

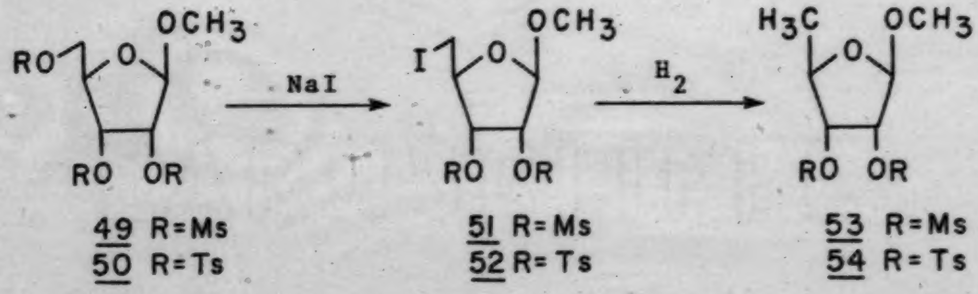
known 5-O-benzoate [56] (44) with 0.1 N sodium methoxide proceeded smoothly to give the deblocked derivative (45) in 95% yield. The hydroxyl function produced a broad band at 3400 cm^{-1} in the infrared spectrum as well as an exchangeable proton in the PMR spectrum. As will be seen for most of the imidazolidine sugars, the parent ion in the mass spectrum is often accompanied by satellites at M^++1 and M^+-1 as well as a fragment corresponding to M^+-NC_6H_5. In the case of 45, molecular ions were observed at m/e 397 (M^++1), 396 (M^+) and 395 (M^+-1). The peak at m/e 381 (M^+ - CH_3) was a predominate feature and was generally observed for isopropylidene protected sugars. For all the imidazolidine sugars, cleavage at the C-glycosyl bond led to a strong base peak at m/e 223 which was definitive for the ionized imidazolidine ring. The remaining characteristic ion was m/e 290 ($M^+ - CH_3 - NC_6H_5$). As previously described for the imidazolidine derivatives, hydrolysis was accomplished using three equivalents of p-toluenesulfonic acid. Contrary to the case where benzoyl protecting groups were present, hydrolysis of 45 was complete in five to ten minutes compared to one hour for 23. This could possibly result from intramolecular assistance of the free 5-OH in the hydrolysis of 45. Filtration to remove the diamine p-toluensulfonate salt and evaporation of the solvent gave crude 27 directly in quantitative yield. Chromatography of this product on silica gave an 80% yield of the homogeneous allose derivative which was crystallized from chloroform-hexane to give crystalline 27 in approximately 70% yield. Although the melting point of 27 was lower than reported [80] and showed some softening from 150-160°C, all of the other physical data including PMR and IR spectra and elemental analyses indicated this material to be structure 27. The mass spectrum gave a parent peak at m/e 202 (M^+) as well as m/e 187 ($M^+ - CH_3$) which was characteristic for an isopropylidene protected derivative. A preliminary reaction of 27 with sodium cyanide and potassium carbonate in water gave an unstable intermediate 46 that was hydrolysed using hydrogen peroxide. The product of this reaction was assumed to be 46a, which was very soluble in water. Even employing continuous extraction with ethyl acetate it was difficult to recover the product. Alternately, as shown in Scheme III, the reaction of 27 with benzylamine hydrochloride and sodium cyanide in water initially gave what was presumed to be the α-hydroxy nitrile (46) (TLC, ethyl acetate - hexane (3:1), starting material $R_f = 0.5$, product $R_f = 0.65$). The product was unstable and reverted to starting material if attempts were made to isolate this intermediate.


OH
NaCN
CN
OH
HO
H_2O_2
CONH2
OH
HO
27
46
46a
HC=O
HO
NaCN
BnNH2
CN
NHCH2C6H5
HO
H_2O_2
CONH2
NHCH2C6H5
HO
27a
47
48

SCHEME III

However, if the solution was heated to 80°C for one hour, a faster moving product was observed by TLC (ethyl acetate - hexane (3:1), $R_f = 0.8$). This product was isolated and shown by PMR spectroscopy to have incorporated the benzylamine function. The mass spectrum had a peak at m/e 291 (M^+-HCN) and 276 (M^+-HCN-CH_3). Although this information was not definitive for the structure of the proposed intermediate 47, further reactions indicated that it was likely so. In the continuing preparation of the α-benzylamino amide, this intermediate (47) was not isolated but hydrolysed directly with alkaline hydrogen peroxide. In this manner the α-benzylamino amide (48) was isolated in 50 - 55% yield from 27. Presumably the initial product 46 reverted to the aldehyde 27a which then reacted with benzylamine and sodium cyanide to give 47. Hydrolysis of this material gave 48. The data obtained from the proton NMR and mass spectra indicated that both the benzylamino and amide functions were present. The D_2O exchangeable PMR signals between δ 6-7 were typical for amide protons. Ion peaks at m/e 321 (M^+-CH_3), 292 (M^+-$CONH_2$) and 230 (M^+-NHC_7H_6) provided further indicative evidence. Prolonging the time or increasing the temperature for the reaction with sodium cyanide and benzylamine did not increase the yield of 47. Presumably the basic conditions at elevated temperature leads to degradation and possibly epimerization of the intermediate aldehyde. In view of the poor yields and required unfavorable reaction conditions, investigations of this route were not continued.

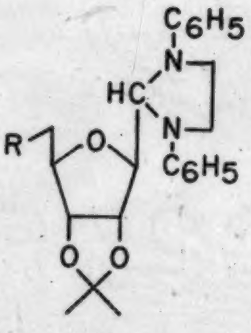
During the course of these exploratory studies several model reactions were investigated for introduction of the 5-deoxy and the 2,3-unsaturated functions into a carbohydrate derivative. The tri-mesyl (49) as well as the tri-tosyl derivative (50) of methyl β-D-ribofuranoside were studied to determine the reaction conditions for formation of a 5-deoxy derivative,[147,147a] as shown in Scheme IV. Reaction of 49 or 50 with sodium iodide in dimethylformamide gave the 5-iodo derivatives (51) and (52), respectively, in essentially quantitative yields. It was evident from the proton NMR spectrum of 51, which gave only two mesyl group signals as well as an upfield shift for the C_5 protons, that only the primary mesyl group had been displaced. The reaction with secondary mesyl groups apparently required more



SCHEME IV

drastic conditions. These derivatives 51 and 52, were readily hydrogenated using 5% Pd-C to give 53 and 54 in quantitative yield. The PMR doublet at δ 1.45 (J_{5-4} = 6 Hz) for 53 and δ 1.10 (J_{5-4} = 7 Hz) for 54 together with the quartet observed for H_4 were consistent with a 5-deoxy(4-methyl) function.

Also used as a model compound was the previously described imidazolidine derivative (45). Initial attempts were made to prepare the 5-iodo derivative (55a) from



55

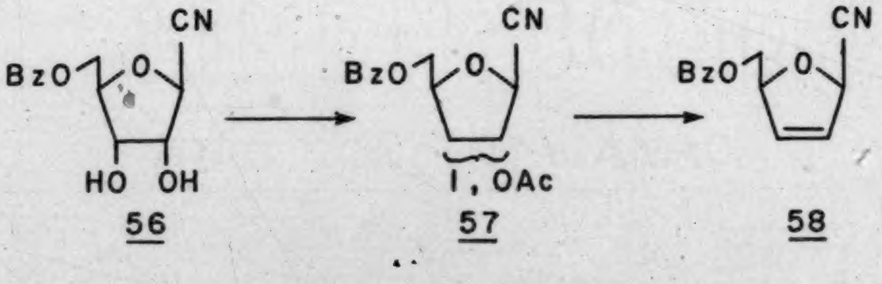
55a R = I
b R = OMs
c R = Cl
d R = H

45 using methyltriphenoxy phosphonium iodide.[148] This reaction gave a low yield of a product that migrated faster than the starting material on TLC. This material was unstable and decomposed if heated. The 5-mesyl derivative (55b) was prepared by treatment of 45 with methanesulfonyl chloride and pyridine. The three-proton PMR signal at δ 2.80 was typical for a mesyl function. The mass spectrum of 55b had a parent ion

at m/e 474 (M^+) as well as characteristic degradation ions at m/e 459 (M^+-15), 379 (M^+-OMs), 378 (M^+-1-OMs), and 368 ($M^+-CH_3-NC_6H_5$). The product (55b) was stable when isolated as a crystalline derivative, but it also decomposed if heated. A low yield of what appeared to be the 5-iodo derivative was obtained by heating 55b with sodium iodide in acetone. A similar reaction attempted in dimethylformamide resulted in decomposition of 55b. Presumably the 5-iodo and mesyl derivatives are unstable due to intramolecular cyclization with the imidazolidine ring. The more stable 5-chloro derivative 55c was obtained in 88% yield by reaction of 45 with triphenylphosphine and carbon tetrachloride.[149] Introduction of the chloro function was apparent upon inspection of the mass spectrum of the product. Molecular ions corresponding to fragments containing ^{37}Cl were observed at m/e 417 (M^+ + 1), 401 (M^+-CH_3), and 340 ($M^+-O_2C(CH_3)_2$) and for ^{35}Cl at m/e 415 (M^++1), 414 (M^+), 399 (M^+-CH_3) and 338 ($M^+-O_2C(CH_3)_3$). This product was readily reduced to the 5-deoxy derivative 55d using tri-n-butyltin hydride.[150-152] As with the previous 5-deoxy models, the doublet at δ 1.2 (J = 7 Hz) in the proton NMR spectrum was typical. The mass spectrum had the parent ion at m/e 380 (M^+) as well as fragments at m/e 379 (M^+-1), 365 (M^+-CH_3) and 274 ($M^+-CH_3-NC_6H_5$).

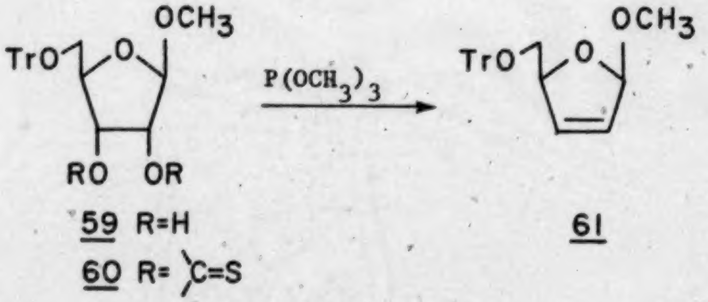
The dimesyl (53) and ditosyl (54) derivatives were then investigated in an effort to introduce 2,3-unsaturation using the general Tipson-Cohen procedure reported by several workers.[153-156] Use of zinc and sodium iodide in refluxing dimethylformamide for one hour gave a dark colored solution. Inspection by TLC revealed only starting material and decomposition material which remained on the base line. Prolonged heating resulted in extensive decomposition. This failure probably resulted from the relative instability of the 5-deoxy derivatives under these forcing conditions and from the difficulty in effecting displacement of a secondary sulfonate group. An attempt to obtain the 2,3-unsaturated derivative by reaction of 53 with sodium and naphthalene [157] led to several unidentified products.

In a different approach the nitrile 56 was



employed as a model. Treatment of this vicinal diol with α-acetoxyisobutyryl chloride and sodium iodide in acetonitrile[158] gave a good yield of the iodo-acetate 57. Reductive elimination to give the unsaturated derivative 58 (~60%) was effected with zinc-copper in acetic acid and water. This sequence for conversion of vicinal diols to unsaturated derivatives is being investigated in this laboratory.[158a] These reaction conditions however, were anticipated to be too acidic for intermediates in the synthesis of furanomycin. The identical unsaturated product (58) was obtained by the method of Hannessian and co-workers,[159] by treatement of the *N*,*N*-dimethylaminomethylidene acetal of 56 with methyl iodide. This procedure gave a low yield (20%) of 58. This product was assumed to be the unsaturated derivative by inspection of the PMR data. The ABX splitting pattern at δ 6.05 for H_3 and H_4 as well as the multiplets at δ 5.22 (H_5) and δ 5.48 (H_2) were typical for a 2,3-unsaturated pentofuranose. Similar patterns were observed for these types of derivatives as will be described later.

These exploratory approaches were abandoned upon the finding that thiocarbonate derivatives of model furanose sugar derivatives were readily converted to unsaturated products with trimethyl phosphite as first described by Corey and Winter.[160] Initially the thiocarbonate function was introduced by heating a solution of the vicinal diol with bis-imidazole thiocarbonate [161] in dimethylformamide. Subsequently this reaction was more conveniently performed in acetone at room temperature. Treatment of the 5-O-trityl derivative [162,163] (59) with bis-imidazole thiocarbonate in DMF at 90°C for three hours gave 60 (91%) as shown in Scheme V. This product was relatively insoluble in most organic solvents as were several other sugar thiocarbonate derivatives. It was possible to crystallize this product in approximately 60% yield from dimethylformamide - ethanol. The mass spectrum gave a parent ion at m/e 448 (M^+). As will be seen later, all of the thiocarbonate derivatives were easily characterized from the spectral data. The proton NMR spectra showed definite downfield shifts for the sugar protons attached to the ring carbons on the cyclic thiocarbonate function. Also a UV absorption at 238 nm was characteristic for this group. Treatment of 60 with trimethylphosphite at reflux for seven hours gave 61 in 90% yield after chromatography. The crystalline



59 R=H

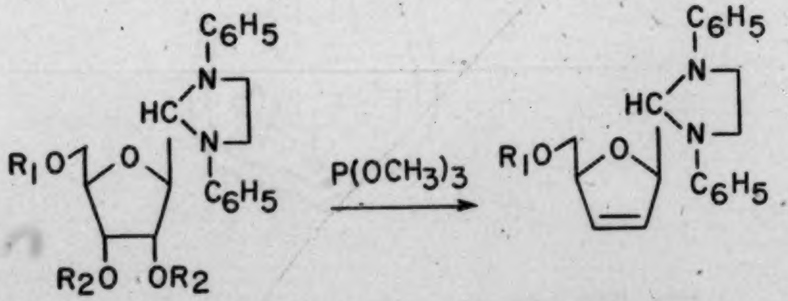
60 R= >C=S

61

SCHEME V

product melted at 87 - 88°C as compared to the literature[163] value of 82 - 83°C. The specific rotation observed was $[\alpha]_D^{23}$ - 88° compared to the reported value[163] of -72°. Inspection of the ^1H NMR spectral data indicated an ABX pattern centered at δ 5.9 (H_2,H_3) and multiplets at δ 6.1 (H_1) and δ 4.8 (H_4) similar to that described previously[163] and for 58.

The same series of reactions was then applied to the imidazolidine derivative[56] (62) as shown in Scheme VI. Reaction of the imidazolidine sugar with trityl chloride in pyridine was observed to be incomplete after several days at room temperature. However, the dimethoxytrityl or trityl derivative was formed in good yield using dimethoxytrityl chloride or trityl bromide, respectively, at 60 - 70°C for one hour. In



62 $R_1=R_2=H$

63 R_1=dmTr $R_2=H$

64 R_1=Tr $R_2=H$

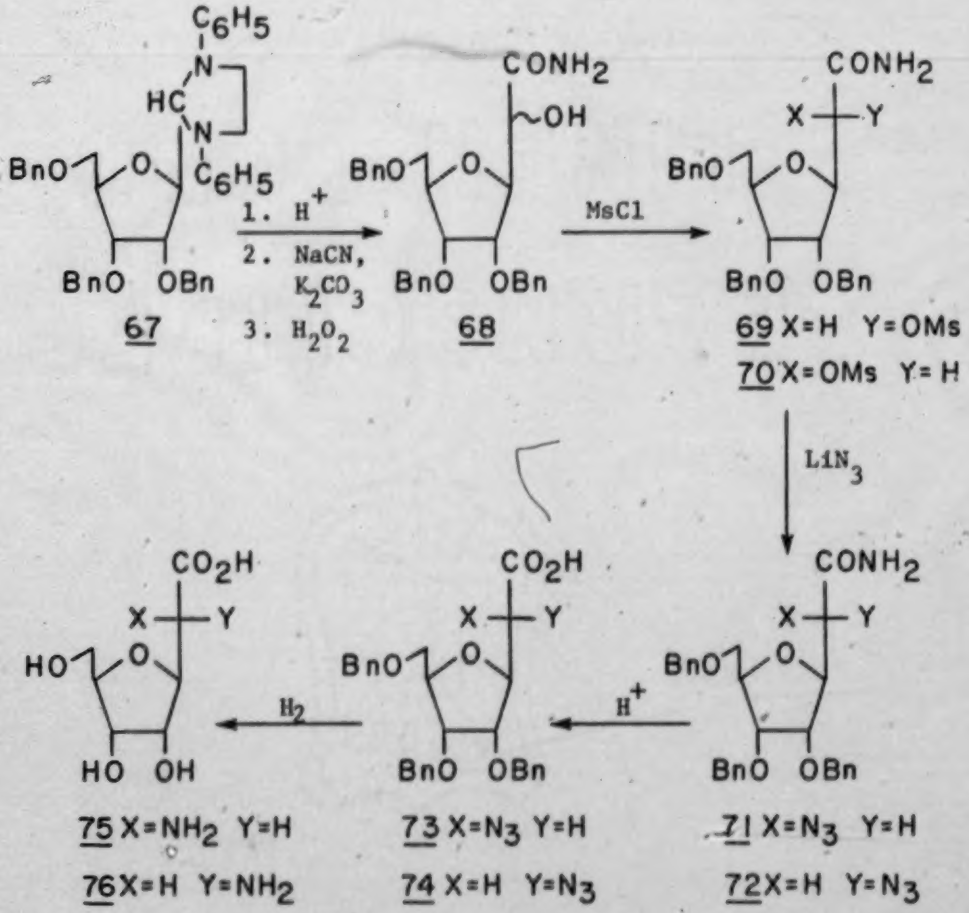
65 R_1=Tr R_2= >C=S

66 R_1=Tr

SCHEME VI

this manner both 63 and 64 were isolated in approximately 90% yield after chromatography. The trityl derivative (64) consistently gave better yields, and could be isolated with only minor traces of impurities as detected by TLC. The highest observed fragments in the mass spectrum were m/e 580 (M^+-H_2O) and 562 (M^+-2H_2O). This intermediate gave a single product that was homogeneous by TLC upon treatment with bis-imidazole thiocarbonate in acetone. The resulting thiocarbonate (65) was isolated in a crude yield of 93%. Introduction of the thiocarbonate function was observed to shift H_3 and H_4 downfield in the PMR spectrum and gave rise to a distinct UV absorption at 238 nm. Although no parent ion was observed for 65 in the mass spectrum, the fragment at m/e 580 was assigned to $M^+-OC=S$. Traces of imidazole present with the product were difficult to remove. Since this seemed to have no effect on the subsequent reaction, 65 was treated with trimethylphosphite at reflux for eight hours without further purification. The unsaturated product 66 was isolated in 93% yield. The data obtained from elemental analysis, the mass spectrum and the PMR spectrum were all consistent with the proposed structure of 66. The chemical shifts, the ABX splitting pattern centered at δ 5.83 and the multiplets at δ 5.25 (H_2) and δ 4.90 (H_5) were very similar to those for 61 and 58.

The first approach we employed which resulted in the formation of α-amino acids began with the imidazolidine sugar [56,57,66] 67 as shown in Scheme VII. This

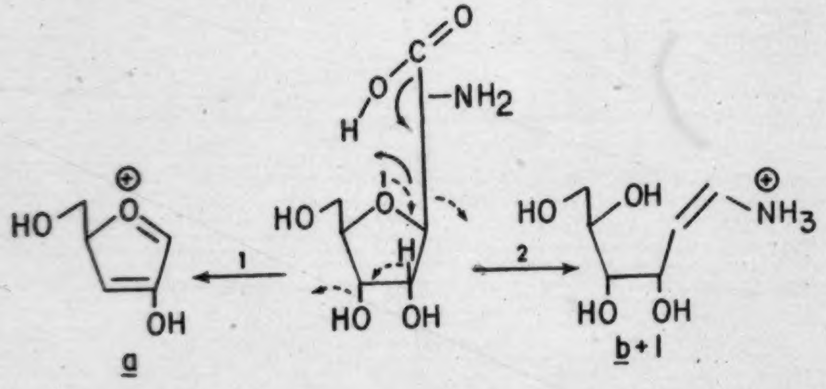

C_6H_5
HC
N
C_6H_5
BnO
O
OBn
67
1. H^+
2. NaCN, K_2CO_3
3. H_2O_2
$CONH_2$
OH
68
MsCl
69 X=H Y=OMs
70 X=OMs Y=H
LiN_3
71 X=N_3 Y=H
72 X=H Y=N_3
H^+
CO_2H
73 X=N_3 Y=H
74 X=H Y=N_3
H_2
HO
OH
75 X=NH_2 Y=H
76 X=H Y=NH_2

SCHEME VII

derivative was used by Moffatt as an intermediate in the synthesis of several C-nucleosides.[56-58] Hydrolysis of the aldehyde protecting group of 67 using p-toluenesulfonic acid was originally reported on a two mmole scale.[57] This reaction was readily scaled up to ten mmoles with high yield (~90%) of 68 obtained. Examination of this product by TLC revealed only a trace of faster moving impurities and it was therefore used without further purification. Treatment of 68 with methanesulfonyl chloride in pyridine for seven hours at 0° gave 69 and 70 which were isolated as a solid mixture. It appeared that longer reaction times resulted in decreased yield. Fortuitously it was found that the isomers could be separated at this point by triturating the solid mixture with hot ether. The insoluble solid remaining (43%) was the faster migrating isomer on TLC (chloroform-ethyl acetate (1:1), $R_f = 0.50$) and was tentatively assigned as structure 69. Chromatography of the trituration mother liquors gave a slower isomer 70 (38%, $R_f = 0.47$), with a trace (~5%) of the faster isomer. These two isomers were readily distinguished by proton NMR spectroscopy. The faster isomer gave a signal for the mesyl group at δ2.91, compared to 2.86 for the slower isomer. The signal for H_2, δ 4.90 (J_{2-3}= 5 Hz) for the faster isomer and δ 4.91 (J_{2-3}= 4 Hz) for the slower isomer was shifted downfield relative to that for the hydroxy precursor 68. It appears that 69 and 70 have sufficiently restricted conformations that the splitting patterns for H_7 and $H_{7'}$ of each isomer were different. The pseudo octet centered at ~δ 3.57 with $\underline{J}_{7-7'}$ = 10 Hz, $\underline{J}_{7-6}$ = 3 Hz and $\underline{J}_{7'-6}$ = 2.5 Hz for the faster isomer was clearly different from the corresponding multiplet of the slower isomer centered at ~δ 3.55 with $\underline{J}_{7-7'}$ = 11 Hz, $\underline{J}_{7-6}$ = 4 Hz, $\underline{J}_{7'-6}$ = 3.5 Hz. The infrared spectrum of 69 or 70 had a band at 1650 cm^{-1}, typical for an amide carbonyl stretching frequency. This band was observed for all the subsequently described amide derivatives. The mass spectral fragmentation was similar for both isomers. A parent ion was observed with 69 or 70 at m/e 555 (M^+) as well as an M^++1 ion at m/e 556. Such ions appear to be common for most of the α-substituted amides prepared. Other characteristic ions were noted at m/e 476 (M^+-SO_2CH_3) and 464 (M^+-$CH_2C_6H_5$). Either of these mesyl derivatives was readily subject to displacement with lithium azide in dimethylformamide to give 71 or 72 in approximately 90% yield. Similar treatment with sodium azide gave almost no reaction products. It was later discovered that an analogous sequence had been applied earlier by Moffatt and co-workers [130] to prepare polyoxin analogues. A chemical proof was presented [130] to show that the displacement proceeded with inversion of configuration to give the α-azido amide. It is assumed that the same is true in the present case although no chemical proof was undertaken.

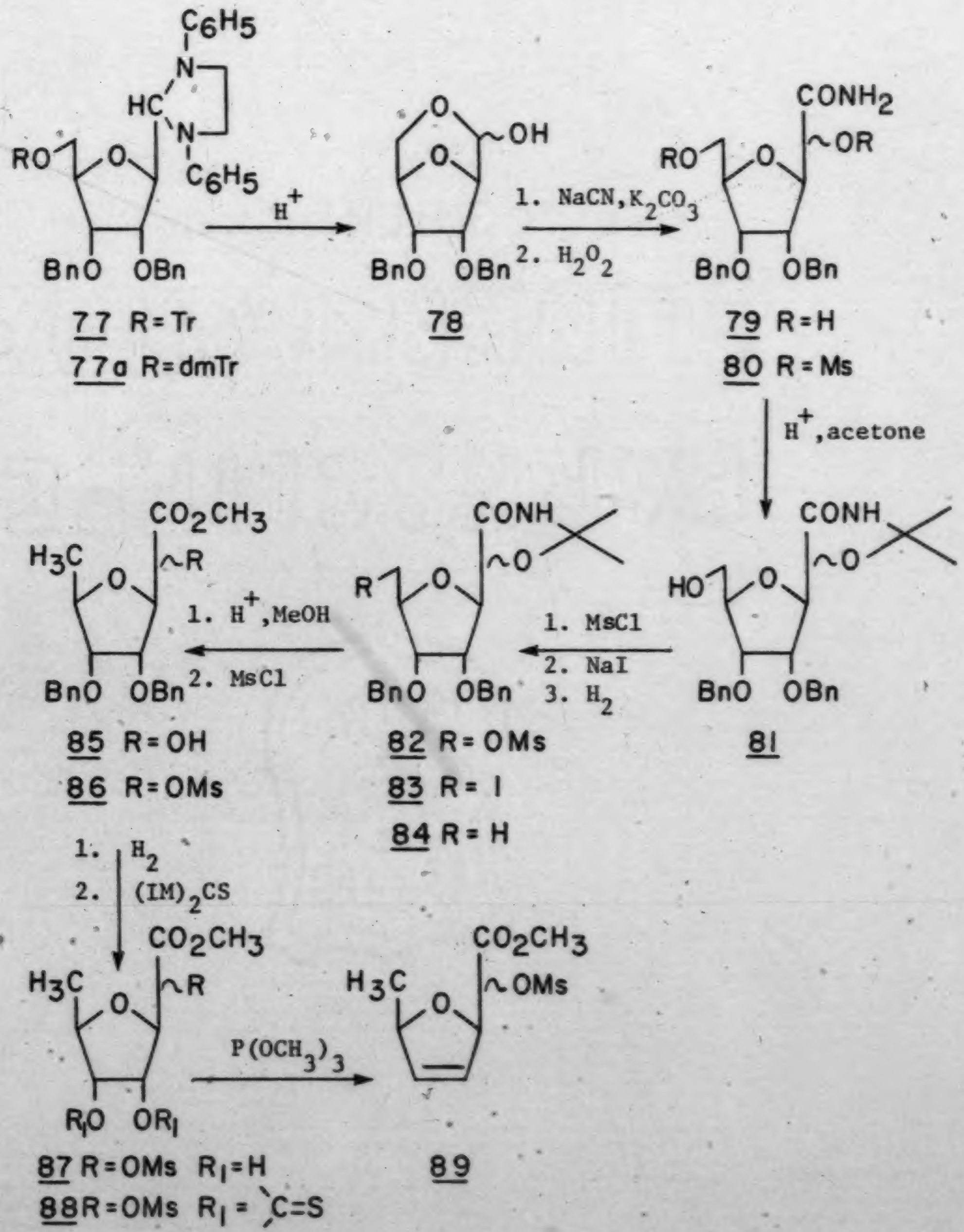
Supporting evidence for this assumption comes from the ^1H NMR spectral information. The loss of the mesyl signals as well as the upfield shift of the H_2 proton indicated that the mesyl function had been displaced. Moreover, the splitting patterns for H_7 and $H_{7'}$ of 71 centered at δ 3.46 and 3.57 with $\underline{J}_{7-7'}$ = 10 Hz, $\underline{J}_{6-7}$ = 4 Hz, $\underline{J}_{6-7'}$ = 3.5 Hz and of 72 centered at δ 3.52 and 3.60 with $\underline{J}_{7-7'}$ = 10 Hz, $\underline{J}_{6-7}$ = 3.5 Hz, $\underline{J}_{6-7'}$ = 4 Hz, appear to correspond closely with those of 70 and 69, respectively. The IR spectra of both 71 and 72 had a strong band at 2120 cm^{-1} (N_3). It is also interesting that the order of melting points for 69 (173 - 174°C) and 70 (114 - 115°C) is reversed for 71 (93 - 94°C) and 72 (155 - 156°C). One would expect that the relative values of optical rotation would also be interchanged. However, the values for 69 (+65°) and 70 (+30°) compared to 71 (+13°) and 72 (+10°) are inconclusive owing to the small and similar dextrarotatory values for the latter pairs.

Further modifications of the α-azido amides were then investigated. Solvolysis of the amide function directly to the ester was accomplished in over 90% yield by refluxing the amide in dry methanol over ANGC(H^+) resin. Alternatively, treatment of 71 or 72, in a mixture of hydrochloric acid-water-1,4-dioxane at 80°C for eighteen hours gave quantitative hydrolysis to the syrupy acid 73 or 74. Reduction of the azide function was readily accomplished with 5% Pd-C at atmospheric pressure. The α-amino ester obtained in this manner from the α-azido ester proved to be unstable at room temperature. The initial product was slowly converted to an unidentified product. It was presumed that intermolecular dimerization to the piperazine derivative could account for this observation. This route was not pursued further. As expected, hydrogenation of the α-azido acids 73 or 74 gave the corresponding α-amino acid. These were more stable at room temperature. Complete removal of the benzyl groups presented a more difficult problem. Initially, boron trichoride was used to cleave the benzyl protecting groups.[164,57] This procedure led to the isolation of the debenzylated α-azido amide in approximately 50% yield. This product was identified only by mass spectroscopy, m/e 204 (M^+-N_2), 172 ($M^+-N_3-H_2O$) and 133 ($M^+-CH_3N_4O$) and the IR band at 2140 cm^{-1} (N_3). Alternative attempts at debenzylation employed hydrogenation of 71 or 72 over 5% Pd-C with pressures up to 60 psi in the Parr shaker. This resulted in reduction of the azide group but no debenzylation. However, when this hydrogenation was performed in a high pressure bomb at 100 psi over 5% Pd-C debenzylation was usually complete in 24 to 48 hours. The results were very dependent on the efficiency of stirring as well as the quality of the catalyst. (It was found necessary to wash the catalyst with 1 N HCl and then water followed by drying under vacuum in order to activate the catalyst so that consistent results were obtained.) In view of prior observations involving the chemical transformations on the α-azido amides, 71 or 72 was hydrolysed first, followed by simultaneous hydrogenation of the azide and benzyl groups. Potential racemization during the alternative hydrolysis of an α-amino amide was thereby avoided. The α-azido amides (71) and (72) were hydrolysed in a mixture of hydrochloric acid - water - 1,4-dioxane (1:1:10) at 80°C for 18 hours. Isolation of product gave syrupy 73 and 74, respectively, in quantitative yield. These diastereomeric products were hydrogenated directly in ethanol buffered with 1 M NH_4OAc-HOAc at 100 psi for 48 hours. (The solution was buffered to preclude any problems that might be encountered with traces of acid present either from the previous hydrolysis step or from the acid washed catalyst). When reaction was complete (TLC), the catalyst was filtered and washed with 95% ethanol and then water. The combined filtrates were evaporated to a syrup and applied to a column of ANGC(H^+) resin. Elution with water followed by 0.5 N NH_4OH gave 110 mg (53%) of 75 or 76 as a tan colored solid. This moderate yield probably resulted from the relatively large quantities of catalyst required (~one weight equivalent). It was observed that both the product and starting material were adsorbed to some degree on carbon. The possibility also exists that losses occurred in the previous hydrolysis step. This was not investigated further. Both of the α-amino acids were very soluble in water but sparingly soluble in 95% ethanol. Crystalline *75* was obtained from a mixture of water - 95% ethanol. These fine needle like crystals softened to a glass at 125-130°C and finally decomposed at 207-210°C. Analysis indicated that the compound crystallized as the dihydrate. Drying of the product at room temperature overnight resulted in analyses compatible with a dihydrate. Heating of the compound at 56°C (refluxing acetone) under vacuum for several days gave analyses in agreement with approximately 3/4 mole of water of hydration. This was not confirmed in the usual manner by PMR integration since the H_2O peak was overlapped by sugar protons. No definitive information was obtained from electron impact or chemical ionization mass spectra. The former gave predominate fragments at m/e 116 (84%) and 115 (91%), identified as (*a*). As noted previously (*vide supra*)the chemical ionization mass spectrum had fragments at 164 and 327 which could



correspond to (b + 1) and (2b + 1), respectively. The IR spectrum was typical for an α-amino acid with a strong absorption at 1640 cm^{-1} (CO_2^-), 1500 cm^{-1} (NH_3^+) and a broad band at 3100 - 3400 cm^{-1} (OH, NH_3^+). ORD [165] and CD [166] spectra were used to assign the L or D amino configuration. Inspection of ORD and CD spectra of 75 in 6N HCl gave values calculated as $[\phi]_{225}$ = +2000 and $[\theta]_{210}$ = +2010, respectively. These values are compatible with assignment of 75 as an L α-amino acid. It was found that 76 did not crystallize readily and it was isolated as an amorphous solid that decomposed at approximately 120°C. The compound was assigned the D α-amino acid configuration from the negative values obtained from the ORD($[\phi]_{225}$ = -2,300) and CD($[\theta]_{210}$ = -1,850) spectra. Attempts to form the hydrochloride salts of either 75 or 76 to obtain more crystalline derivatives led to very hygroscopic materials which were difficult to handle. Because of the low overall yields of 75 and 76, it was decided not to pursue this route to furanomycin. Further transformations on the sugar portion of 75 or 76 would require several blocking steps of both the sugar and amino acid functions. Reaction schemes incorporating the necessary sugar transformations before introduction of the α-amino acid function appeared more feasible. In view of experience gained in these exploratory studies, the following scheme was envisioned: 1) formation of the C-glycosyl component, 2) deoxygenation to the 7-deoxy function, 3) introduction of the α-mesyl and α-azido amide function, 4) solvolysis of the amide to the ester, 5) transformation of the vicinal diol to the 4,5-unsaturated derivative.

Initially, only limited success was achieved in obtaining the required C-glycosyl derivatives by the method previously described for the tri-O-benzyl α-hydroxy amide (68). Using the modified Strecker type synthesis, the α-hydroxy amides derived from isopropylidene allose (27) or from the aldehydes generated from the 5-chloro (55c) and 5-deoxy (55d) imidazolidines, were too water soluble to be isolated efficiently. These results indicated that a base stable, hydrophobic blocking group would be advantageous to allow the product to be easily extracted from the basic aqueous solution. In addition, the blocking groups were selected so that the hydroxy group at C_7 could be selectively deprotected. It was decided that 5-O-trityl and 2,3-di-O-benzyl protecting groups would satisfy the above requirements. Treatment of 5-O-trityl imidazolidine (64) or the 5-O-dimethoxytrityl imidazolidine (63) with sodium hydride and benzyl bromide in dimethylformamide gave the desired dibenzyl derivatives 77 and 77a, respectively. In subsequent reactions 77 was used since it was purified more readily than 77a. Purified 77 was isolated as a foam after chromatography and was characterized by its mass spectrum which had a parent ion at m/e 778 (M^+) and major fragment ions at m/e 670 (M^+-HOBn) and 562 (M^+-2HOBn). As indicated in Scheme VIII, treatment of the imidazolidine (77) with p-toluenesulfonic acid gave 78 as a syrup in 82% yield after chromatography. The PMR spectrum had no signal for an aldehyde proton, normally found at δ 10 - 11, and the IR spectrum had no absorption band in the aldehyde region (1720-1740 cm^{-1}). It was assumed that 78 existed in the hemiacetal form analgoues to the behavior of 27. The mass spectrum of 78 had a parent ion at m/e 342 (M^+) and major fragment ions at m/e 251 ($M^+-CH_2C_6H_5$), 235 ($M^+-OCH_2C_6H_5$) and 234 ($M^+-HOCH_2C_6H_5$). In contrast to the acyclic free aldehyde forms, the hemacetals 78

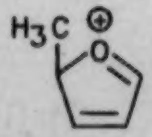

C6H5
HC
N
N
C6H5
RO
O
BnO OBn
77 R=Tr
77a R=dmTr
H+
O
O
OH
BnO OBn
78
1. NaCN,K2CO3
2. H2O2
CONH2
~OR
RO
O
BnO OBn
79 R=H
80 R=Ms
H+,acetone
CONH
~O
HO
O
BnO OBn
81
1. MsCl
2. NaI
3. H2
CONH
~O
R
O
BnO OBn
82 R=OMs
83 R=I
84 R=H
1. H+,MeOH
2. MsCl
CO2CH3
H3C
~R
O
BnO OBn
85 R=OH
86 R=OMs
1. H2
2. (IM)2CS
CO2CH3
H3C
~R
O
R1O OR1
87 R=OMs R1=H
88 R=OMs R1= C=S
P(OCH3)3
CO2CH3
H3C
~OMs
O
89

SCHEME VIII

and 27 appear to be quite stable for extended periods of time. Intermediate 78 was treated with sodium cyanide and potassium carbonate in 1,4 dioxane-water to presumably give the unstable α-hydroxy nitrile intermediate. This product was isolated as the α-hydroxy amide (79) after hydrolysis with hydrogen peroxide. The yield of 79 from the imidazolidine (77) was 76%. Attempts to fractionally crystallize the diastereomeric mixture of α-hydroxy amides were unsuccessful. In subsequent reactions a mixture of the allo and altro isomers of 79 were used. It was hoped that the 7-mesylate group of the 2,7-di-O-mesyl derivative 80 could be selectively displaced by iodide and thereby bypass several blocking steps. Unfortunately it appeared that the reactivity of the 2-O-mesyl function lay between that of a primary and "normal" secondary mesyl derivative. Consequently, treatment with sodium iodide resulted in displacement at the secondary C-2 position as well as at the primary C-7 position. Initial blocking of the 2-hydroxy group therefore appeared to be necessary. Treatment of 79 with acetone and perchloric acid gave 81 which was characterized by its mass spectrum with characteristic ions at m/e 428 ($M^+ + 1$), 412 (M^+-CH_3) and 336 ($M^+-CH_2C_6H_5$). This product was isolated as a syrup and was treated directly with methanesulfonyl chloride in pyridine to give the 7-O-mesyl derivative

(82) in 92% overall yield from 79. Inspection of the proton NMR spectrum revealed that 82 was a diastereomeric mixture (at C-2). The exchangeable (isopropylidene) amide protons of each C-2 epimer of 82 appeared as a broad singlet. The ratio of these distinct signals corresponds to that of the respective three-proton mesyl singlet. The amide proton signal for 82 was shifted downfield by ~δ1.5 from that of the amide protons of the free amide 80. The mass spectrum of 82 had several characteristic peaks such as me/ 506 ($M^+ + 1$), 505 (M^+), 491 ($M^+ + 1-CH_3$), 490 (M^+-CH_3), 415 ($M^+ + 1 - CH_2C_6H_5$), 414 ($M^+-CH_2C_6H_5$), 400 ($M^+ + 1 - CH_3-CH_2C_6H_5$) and 399 ($M^+ - CH_3-CH_2C_6H_5$). The mesylate function of 82 was easily displaced using sodium iodide in methyl ethyl ketone to give the 7-iodo intermediate 83. This product was identified by its mass spectrum with ions at m/e 538 ($M^+ + 1$), 537 (M^+), 523 ($M^+ + 1-CH_3$) and 522 (M^+-CH_3). Reduction of 83 with hydrogen over 5% Pd-C gave the 7-deoxy derivative 84 in 82% overall yield from 82. Proton NMR spectroscopy showed a characteristic doublet at δ 1.25 ($\underline{J}_{7-6}$ = 6 Hz) for the 7-deoxy function of 84. The mass spectrum had a parent ion at m/e 411 (M^+) and ions at m/e 396 (M^+-CH_3) and 320 ($M^+-CH_2C_6H_5$).

Because of the known instability of 5-deoxy sugars towards acid hydrolysis[167] a mild method was required for solvolysis of the amide and isopropylidene functions. Treatment of 84 with ANGC(H^+) resin in methanol removed the isopropylidene protecting group with concomitant conversion of the amide function to a methyl ester to produce 85 in 70% yield. The ^1H NMR spectral data clearly showed this product to be a mixture of diastereomers. This was apparent in the two sets of doublets for H_7 at δ 1.16 and 1.19 and in the singlets for the methyl ester groups at δ 3.62 and 3.72. The exchangeable α-hydroxy proton appeared at δ 2.95. The IR spectrum had bands at 1745 cm^{-1} (CO_2Me) and 3540 cm^{-1} (OH). A parent ion at m/e 386 (M^+) and a fragment ion at m/e 295 ($M^+-CH_2C_6H_5$) were present in the mass spectrum. Reaction of 85 with mesyl chloride in pyridine gave the α-mesylate 86 in 88% yield. Introduction of this group led to the appearance of new three-proton singlets at δ 3.14 and δ 3.68 in the PMR spectrum. The highest identifiable fragment in the mass spectrum of 86 was at m/e 373 ($M^+-CH_2C_6H_5$). The benzyl protecting groups were readily hydrogenolized over 5% Pd-C to give 87 in quantitative yield. This product was used without further purification to form the thiocarbonate derivative 88 employing bis-imidazole thiocarbonate in acetone. Purification by chromatography gave the desired product 88 as a syrup in 99% yield. The proton NMR spectrum of 88 gave a familiar pattern with a downfield shift for the sugar protons H_4 and H_5. Mass spectral data included a parent ion at m/e 326 (M^+). Formation of the 4,5-unsaturated product 89 was effected in 82% yield after chromatography by refluxing 88 with trimethylphosphite for four hours. One of the diastereomers fractionally crystallized from ether-skelly "B". All of the physical data were consistent with the proposed structure 89. The ^1H NMR spectrum showed a pattern similar to that previously described for the 2,5-dihydrofuran derivatives 58, 61 and 66. The only useful information extracted from the mass spectral data was the base peak fragment postulated as (c), which corresponded to m/e 83. The

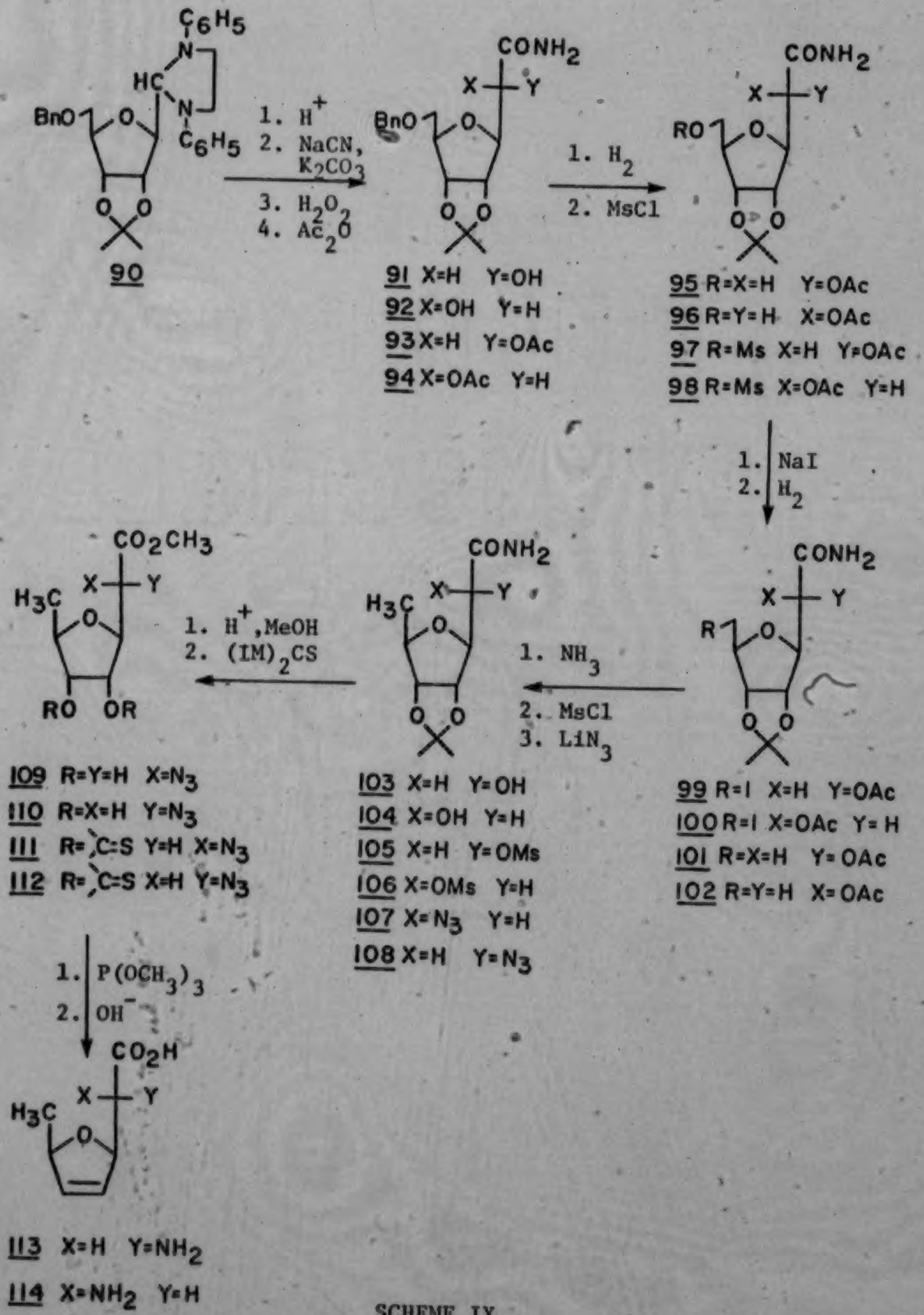


c

chemical ionization (NH_3) mass spectrum had ions at 268 (M^+ + 18) and 518 (2M + 18). Displacement of the mesylate group with azide proved to be more difficult than anticipated. Treatment of 89 with lithium azide in dimethylformamide under a variety of conditions resulted in decomposition. A similar attempt using tetramethylguanidinium azide produced less decomposition but still did not give satisfactory results. Evidently the amide function is essential for smooth displacement of the α-mesyl derivative. The same observation had been noted by other workers [168] in displacements of α-mesyl or α-tosyl esters with azide. They reported low yields as well as racemization accompanying formation of the α-azido esters.

These results indicated that the azide function should be introduced before the amide group was solvolysed. Benzyl protecting groups are incompatible with such a sequence since hydrogenolysis of the benzyl groups would result in simultaneous reduction of the azide function to an amine. Additional steps involving protection of the free amine would then be necessary before further transformations were possible. It was concluded that the acid labile isopropylidene protecting group would be more suitable for the vicinal diol function. This involved a repetition of the same overall reaction sequence starting with the readily available isopropylidene imidazolidine sugar derivative 45. However, the α-hydroxy amide derived from 45 had previously been observed to be too water soluble to be synthetically useful. It was expected that the 6-O-benzyl derivative of 45 could be transformed to the required hydrophobic α-hydroxy amide. Treatment of 45 with sodium hydride and benzyl bromide in dimethylformamide gave the previously unreported imidazolidine 90 in excellent yield (91%). This compound was identified by elemental analysis and mass spectrometry. A parent ion at m/e 486 (M^+) and fragments at 471 (M^+-CH_3) and 380 ($M^+-CH_3-NC_6H_5$) were observed. As shown in Scheme IX, hydrolysis of 90 using p-toluenesulfonic acid, followed by reaction of the intermediate aldehyde with sodium cyanide, potassium carbonate and hydrogen peroxide gave a mixture of 91 and 92 in 86% yield. It was expected from previous experience that this diastereomeric mixture of α-hydroxy amides could be separated. Fractional crystallization from ether gave the faster migrating isomer on TLC (ethyl acetate, R_f = 0.3) in 43% yield. This was tentatively assigned structure 91. The second isomer was obtained as a syrup in 43% yield and was designated structure 92. The presence of the hydroxy and amide functions were confirmed by IR spectroscopy. The mass spectra had peaks at m/e 338 ($M^+ + 1$), 337 (M^+) and 323 ($M^+ + 1-CH_3$).

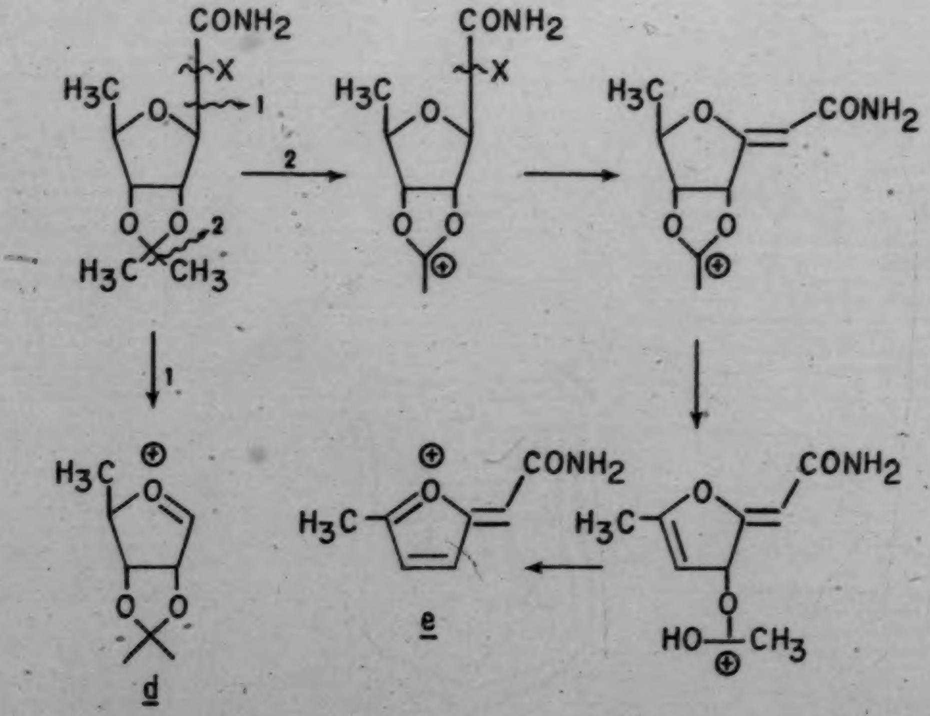
It is interesting that in the subsequent sequence of reactions, the derivatives of 91 were usually isolated as solids and those of 92 were obtained as syrups. Both 91 and 92 were converted to the acetates 93 and 94 in quantitative yield, respectively, using acetic anhydride in pyridine. The proton NMR spectra clearly showed the presence of an acetyl function with a three-


C6H5
N
HC
N
C6H5
BnO
O
O O
90
1. H+
2. NaCN, K2CO3
3. H2O2
4. Ac2O
CONH2
X Y
BnO
O
O O
91 X=H Y=OH
92 X=OH Y=H
93 X=H Y=OAc
94 X=OAc Y=H
1. H2
2. MsCl
CONH2
X Y
RO
O
O O
95 R=X=H Y=OAc
96 R=Y=H X=OAc
97 R=Ms X=H Y=OAc
98 R=Ms X=OAc Y=H
1. NaI
2. H2
CONH2
X Y
R
O
O O
99 R=I X=H Y=OAc
100 R=I X=OAc Y=H
101 R=X=H Y=OAc
102 R=Y=H X=OAc
1. NH3
2. MsCl
3. LiN3
CONH2
X Y
H3C
O
O O
103 X=H Y=OH
104 X=OH Y=H
105 X=H Y=OMs
106 X=OMs Y=H
107 X=N3 Y=H
108 X=H Y=N3
1. H+,MeOH
2. (IM)2CS
CO2CH3
X Y
H3C
O
RO OR
109 R=Y=H X=N3
110 R=X=H Y=N3
111 R=C=S Y=H X=N3
112 R=C=S X=H Y=N3
1. P(OCH3)3
2. OH−
CO2H
X Y
H3C
O
113 X=H Y=NH2
114 X=NH2 Y=H

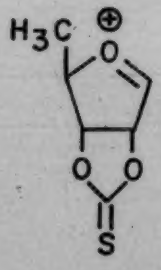
SCHEME IX

proton singlet at δ 2.06 for the faster migrating isomer and δ 2.08 for the slower isomer. The IR spectra gave absorption bands at 1750 cm^{-1}, indicative of an ester group. The mass spectra had ions at m/e 379 (M^+), 364 (M^+-CH_3) and 258 ($M^+-CH_3-OCH_2C_6H_5$). Hydrogenolysis of either derivative over 5% Pd-C gave the deprotected hydroxy derivatives 95 and 96 in quantitative yields. These derivatives were identified by their mass spectra with ions at m/e 290 ($M^+ + 1$), 275 ($M^+ + 1-CH_3$), 274 ($M^+ - 15$) and 232 ($M^+ + 1-CH_3-COCH_3$). It should be noted that care must be taken to monitor this hydrogenolysis reaction by TLC (ethyl acetate, starting material, R_f = 0.79; product R_f = 0.25). The reaction is sensitive to traces of acid and also appears to be concentration dependent. After evaporation of the solvent the product was used without further purification. Treatment of crude 95 and 96 with mesyl chloride in pyridine gave the 7-O-mesyl derivatives 97 and 98, respectively, in 88% yield. The new mesyl signals in the PMR spectra appeared at δ 3.06 for the faster migrating isomer and δ 3.04 for the slower isomer. Major ions identified in the mass spectrum were at m/e 368 ($M^+ + 1$), 353 ($M^+ + 1-CH_3$), 352 (M^+-CH_3), 323 (M^+-CONH_2), 310 ($M^+ + 1-CH_3-COCH_3$) and 308 ($M^+-CH_3-CONH_2$). These mesyl derivatives (97 and 98) were converted to the 7-iodo compounds (99 and 100) by treatment with sodium iodide in 2-butanone. The iodo intermediates were characterized by mass spectral peaks at m/e 385 ($M^+ + 1\text{-}CH_3$) and 384 ($M^+ - CH_3$). Hydrogenolysis of 99 and 100 over 5% Pd-C gave 101 in 94% yield and 102 in 91% yield. The 7-deoxy function was evident from the PMR spectra of 101 and 102 with methyl doublets centered at δ 1.27 (J_{7-6} = 6 Hz) for the faster migrating isomer and δ 1.33 (J_{7-6} = 6 Hz) for the slower isomer. The mass spectrum displayed a familiar pattern with ions at m/e 274 ($M^+ + 1$), 259 ($M^+ + 1\text{-}CH_3$), 258 ($M^+\text{-}CH_3$), 229 ($M^+\text{-}CONH_2$), 216 ($M^+ + 1\text{-}CH_3\text{-}COCH_3$) and 215 ($M^+ - CH_3\text{-}COCH_3$). Although previous derivatives underwent only minor amounts (10-15% of base peak) of C-glycosyl bond rupture, the mass spectra of the 7-deoxy derivatives had substantial fragmentation to an ion idenified as d. Complementary to this fragment was another ion assigned the structure e. As shown below it is postulated that this fragment e was the result of a different fragmentation pathway from that for d. For 101 and 102, d was present in 32% and e in 83% relative intensities.

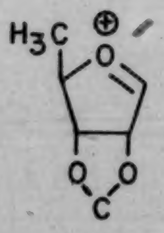
Deacylation of 101 and 102 occurred smoothly in methanolic ammonia to give quantitative yields of 103 and 104. The free hydroxy group was evident in the proton NMR spectrum as an exchangeable doublet at δ 5.7 and from the IR



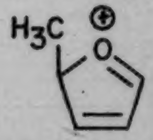
band at 3300-3400 cm^{-1}. Ions in the mass spectra were observed at m/e 232 ($M^+ + 1$), 231 (M^+), 217 ($M^+ + 1 - CH_3$), 216 ($M^+ - CH_3$), 187 ($M^+ - CONH_2$) and 173 ($M^+ + 1 - CONH_2 - CH_3$). Fragment d was present as the base peak and e was present in 56% relative intensity. At this point, both isomers were crystallized and readily characterized by elemental analysis. Treatment of 103 or 104 with mesyl chloride in pyridine gave 105 or 106 in approximately 84% yields. These derivatives gave typical PMR singlet values of δ 3.15 and 3.17 for the mesyl group of the faster and slower migrating isomers, respectively. No parent ions were observed in the mass spectra of 105 or 106. The major fragments present were m/e 294 ($M^+ - CH_3$), d (16%) and e (100%). As expected, displacement of the mesylate function using lithium azide proceeded smoothly in dimethylformamide to give 107 and 108 in 93% yields. The azide group gave rise to a characteristic band at 2120 cm^{-1} in the IR spectrum. The mass spectrum had ion peaks at m/e 241 (M^+-CH_3), 214 (M^+-N_3) and 199 ($M^+-CH_3-N_3$) as well as fragments d (94%) and e (21%). Solvolysis of the amide and isopropylidene functions of 107 and 108 was achieved with ANGC(H^+) resin in methanol to give the methyl esters 109 and 110 in ~85% yields. Both isomers were isolated as syrups after chromatography. The two isomers could be distinguished in the PMR spectrum by the carboxylate methyl signals at δ 3.82 for the faster migrating isomer and δ 3.84 for the slower isomer. The heaviest fragment observed in the mass spectra of 109 and 110 was at m/e 213 (M^+-H_2O). Treatment of the vicinal diols (109 and 110) with bis-imidazole thiocarbonate in acetone gave the thiocarbonate derivatives 111 and 112 in ~92% yield. The ^1H NMR spectra of 111 and 112 again exhibited the familiar downfield shift for the sugar ring protons (H_4, H_5) attached to the thiocarbonate function. The UV absorption for the thiocarbonate derivative was evident at 238 nm. The parent molecular ion of 111 and 112 was the base peak at m/e 273 (M^+). Fragment ions at m/e 159, 127 and 83 were presumed to be f, g and c. These fragments were also observed for



f



g



c

the thiocarbonate 88. The carbenoid type structure in g is an intermediate proposed by Corey [160] in the reductive elimination of thiocarbonates with trialkylphosphites. The thiocarbonate derivatives (111 and 112) proved to be stable when stored at 0°C as a solid. They slowly decomposed at room temperature, especially when allowed to stand in solution.

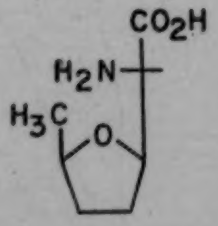
At this point, it was anticipated that reaction of the azide and reductive elimination of the thiocarbonate function could be effected concurrently with trimethylphosphite. It had been reported that azides are reduced to amines by the action of triphenylphosphine [169,170] or trimethylsilyl phosphite.[171]

Vigorous evolution of gas (presumed to be nitrogen) occurred upon dissolving either 111 or 112 in trimethylphosphite. Heating of this solution at reflux for approximately fourteen hours resulted in complete conversion to an unsaturated product. This reaction could not be monitored by silica TLC and detection of the product by sulfuric acid spray. Evidently this was due to the instability of the intermediates. However, a qualitative measure of reaction progress was monitored by UV absorbance. The thiocarbonate starting material is UV absorbing whereas the product is transparent. Complete loss of UV activity indicated the disappearance of starting material. Trimethylphosphite was the solvent-reagent of choice since it has the lowest boiling point (111-112°C) of the readily available trialkylphosphites and can be removed from a reaction by evaporation under vacuum. Complications involving acidic impurities present in commercial trimethylphosphite were avoided by using freshly distilled and dried trimethylphosphite. Hydrolysis of the methyl ester group to give furanomycin (114) was not complete in 1N NaOH overnight at room temperature. Heating this mixture at 90°C for 0.5 hours gave a pale red-orange solution. TLC (nPrOH-H_2O, 7:3) indicated that the reaction was complete. When the initial hydrolysis mixture was heated for 0.5 hours at 90°C, the resulting solution was a dark red color. The saponification solution was adjusted to pH 2 and applied to a column of ANGC(H^+) resin. If the pH of the solution is adjusted to pH 5-7, most of the product is eluted in the aqueous wash along with the methyl phosphates. Presumably this resulted from salt formation involving the α-amino acid and methyl phosphates. This was rectified by acidifying the solution to pH 2, which would result in protonation of the amino acid and more protonation of the methyl phosphates. The separation efficiency was also dependent on the concentration of the applied solution. A dilute solution of the amino acid provided the best separation from the methyl phosphates. The solution was applied to the resin and the column was washed well with water. Subsequent elution with 0.5 N NH_4OH gave the desired product. The ninhydrin positive fractions were collected and evaporated under vacuo to give ~50 mg (32%) of 113 or 114 as a tan colored solid.

The pH of an aqueous solution of the amino acid isolated in this manner was approximately pH 5-6. Contrary to the data reported for the natural antibiotic [36], this synthetic product did not crystallize from water. It was, in fact, quite soluble in water at pH 6.5. Crystallization could not be induced by adjusting the pH of the aqueous solution to the isoelectric point[36] (pH ≈ 5.7). The synthetic product was isolated as a microcrystalline precipitate from acetonitrile-methanol and decomposed at 175-178°C. The natural product was reported to decompose at 220-223°C.[36] The absorption bands in the IR spectrum of the synthetic product at 3000 cm^{-1} (NH_3^+), 1630 cm^{-1} (CO_2^-), 1590 cm^{-1}, 1460 cm^{-1} and 1380 cm^{-1} did not correspond to those reported for furanomycin. The R_f values on TLC (silica gel, solvent M, R_f ≈ 0.4) and paper chromatography (solvent M, R_f ≈ 0.46 and solvent N, R_f ≈ 0.28), were similar to those reported.[36] Cotton effects observed in the CD and ORD spectra of our synthetic product were $[\theta]_{216}$ = +2,200 and $[\phi]_{210}$ = 1,100, respectively. Although these positive values were in agreement with assignment of 114 as an $\underline{\underline{L}}$-α-amino acid,[36,165,166] the elipticity reported for the natural antibiotic was $[\theta]_{210}$ = +26,000. The optical rotation observed for our product ($[\alpha]_D$ = -50°) was also different from that reported ($[\alpha]_D$ = +136).[36] The specific rotation observed upon acidification ($[\alpha]_D$ = -8°, 1N HCl) of our product provided further evidence that 114 is an $\underline{\underline{L}}$-α-amino acid.[172] The proton NMR spectrum of 114 at 100 MHz in D_2O had peaks at δ 1.38 (d, J_{7-6} = 6.5 Hz, 3, H_7), 3.93 (d, J_{2-3} = 3 Hz, 1, H_2), 5.02 (m, 1, H_6), 5.34 (m, 1, H_3), 5.92 and 6.20 (ABX, J_{4-5} = 6 Hz, J_{4-3} = 2Hz, J_{5-6} = 1.5 Hz, 2, H_4, H_5). Additional information on 114 was obtained from its 200 MHz PMR spectrum which had values of δ 1.34 (d, J_{7-6} = 6.5 Hz, 3, H_7), 3.81 (d, J_{2-3} = 3 Hz, 1, H_2), 4.95 (m, J_{6-7} = 6.5 Hz, J_{6-5} = 2 Hz, J_{6-4} = 0.5 Hz, J_{6-3} = 4.5 Hz, J_{6-2} = 0 Hz, 1, H_6), 5.24 (m, J_{3-2} = 3.0 Hz, J_{3-4} = 2.5 Hz, J_{3-5} = 1 Hz, J_{3-6} = 4.5 Hz, 1, H_3), 5.82 and 6.10 (ABX, J_{4-5} = 6 Hz, J_{4-3} = 2.3 Hz, J_{5-6} = 2 Hz, 2, H_4, H_5). The 400 MHz PMR spectrum had peaks at δ 1.34 (d, J_{7-6} = 6.5 Hz, 3, H_7), 3.88 (d, J_{2-3} = 3 Hz, 1, H_2), 5.01 (m, 1, H_6), 5.31 (m, 1, H_3), 5.87 and 6.15 (m, 2, H_4,H_5). The chemical shifts (except for H_7) and coupling constants of our product in most cases were similar to those reported for furanomycin. However, the splitting patterns for H_6 in the PMR spectra were different. Natural furanomycin was observed to have a multiplet (quintet) pattern for H_6 with J_{6-7} = 6.4 Hz, J_{6-5} = 1.9 Hz, J_{6-4} = 1.7 Hz and J_{6-3} = 5.7 Hz. Synthetic 114 displayed a narrow multiplet for H_6 with J_{6-7} = 6.5 Hz, J_{6-5} = 2 Hz, J_{6-4} = 0.5 Hz and J_{6-3} = 4.5 Hz. The ^{13}C NMR spectrum of 114 had seven distinct carbon signals that were assigned as follows, 21.2 ppm (CH_3), 57.4 ppm (C_2), 83.6 and 84.6 ppm (C_3,C_6), 125.1 and 136.0 ppm (C_4,C_5) and 172.0 ppm (CO_2H).

The α-amino diastereomer 113 was easily distinguished from 114 by its physical and spectral properties. This product decomposed at 185-190°C and had an optical rotation of $[\alpha]_D = +21°$. The R_f values on paper chromatography were $R_f = 0.45$ (solvent M) and $R_f = 0.28$ (solvent N). The Cotton effect observed in the CD spectrum was $[\theta] = -1700$. It was estimated by integration of the H_2 signal in the PMR spectrum, that 18% of 114 was present in this sample. The proton NMR spectrum (200 MHz) of 113 had values of δ 1.28 (d, J_{7-6} = 7 Hz, 3, H_7), 3.99 (d, J_{2-3} = 4 Hz, 1, H_2), 5.00 (m, J_{6-7} = 7 Hz), J_{6-5} = 2.5 Hz, J_{6-4} = 1 Hz, J_{6-3} = 4.5 Hz, J_{6-2} = 0 Hz, 1, H_6), 5.30 (m, J_{3-2} = 4 Hz, J_{3-4} = 3 Hz, J_{3-5} = 1 Hz, J_{3-6} = 4.5 Hz, 1, H_3), 5.70 and 6.12 (ABX, J_{4-5} = 6.5 Hz, J_{4-3} = 3 Hz, J_{5-6} = 2.5 Hz, 2, H_4 and H_5). The 400 MHz ^1H NMR spectrum of 113 had values of δ 1.31 (d, J_{7-6} = 6.5 Hz, 3, H_7), 4.01 (d, J_{2-3} = Hz, 1, H_2), 5.02 (m, 1, H_6), 5.32 (m, 1, H_3), 5.72 (d, 1, H_5), 6.14 (d, 1, H_4). The ^{13}C NMR signals of 113 were assigned as follows, 20.9 ppm (C_7), 56.9 ppm (C_2) 84.0 and 83.6 ppm (C_3,C_6), 122.9 and 136.3 ppm (C_4C_5).

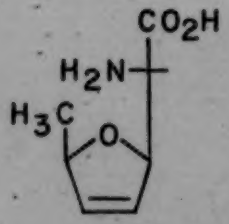
The 4,5 dihydro compound (115) was prepared by hydrogenating a sample of 114 over 5% Pd-C at atmos-



115

pheric pressure for 10 h. The proton NMR spectrum indicated that the major product had values similar to that reported[36] with δ 1.22 (d, 3, H_7), 1.40 - 2.20 (m, 2, $H_{4,5}$), 3.65 (d, 1, H_2), 3.70 - 4.50 (m, 2, $H_{3,6}$). It appears that under these reaction conditions at least three minor byproducts were produced as detected by PMR spectroscopy. This could result from both racemization at C_2 and epimerization at C_3. The CD Cotton effect of 115 (plus byproducts) was $[\theta]_{215}$ = +2,000. The large change in elipticity reported upon reduction of furanomycin ([θ] = +26,000) to dihydrofuranomycin ([θ] = +5,000) was not observed for the conversion of 114 to 115.

It appeared that these discrepancies with the reported data for natural furanomycin could not be accommodated by the reported structure. Coincident with completion of this thesis, a report by M. M. Joullié and co-workers[173] appeared presenting evidence that the structure of furanomycin should be revised to 2(*S*)-amino-2-[2,5-dihydro-5(*S*)-methylfuran-2(*R*)-yl]ethanoic acid (**116**). This *trans* isomer (**116**) has similar but distinguishing properties from the *cis* structure (**114**) reported originally.[36] In private communication with M. M. Joullié, we were provided with information on the physical and spectral data for **116** and **117** prepared by the Ugi four-component-condensation method.[174] The *trans* isomer (**116**) was shown by Joullié to be identical to an authentic sample of furanomycin by melting point, optical rotation, TLC, IR and PMR spectroscopy. The diastereomer **117** was shown to be different from **116** by optical rotation and PMR spectroscopy.



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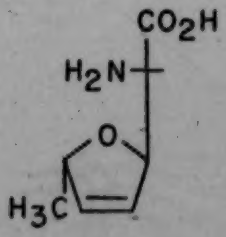

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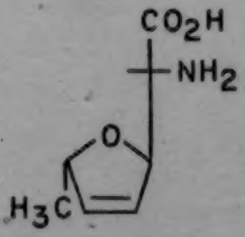

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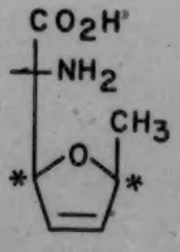
Joullié and co-workers also prepared diastereomeric *cis* isomers **118** and **119** by the Ugi method, but they were unable to assign the absolute stereochemistry at the starred carbons C_3 and C_6. We determined the CD Cotton effects of **116** - **119** with samples kindly provided by Professor Joullié. We found that the elipticity



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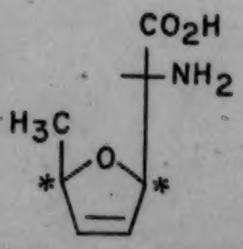


119

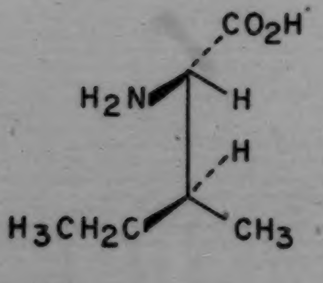
at 210 nm for 116 was $[\theta]_{210}$ = +26,000 as reported for natural furanomycin. Although the CD spectra of many amino acids have definite maxima, none was observed in the spectrum of 116. The reported elipticity value was measured at 210 nm on an inflection of a sharply rising curve of a positive combination Cotton effect. The CD Cotton effect for 117 appeared as a minimum at 220 nm of $[\theta]_{220}$ = -2,900. Normally α-amino acids give rise to a Cotton effect between 210 - 215 nm. The apparent minimum for 117 appears at 220 nm because the true negative extremum is shifted to longer wavelength by a sharply rising positive Cotton effect similar to that observed for 116. This postive Cotton effect could result from an enhanced strong electronic transition occurring in the short wavelength side of 210 nm. It is interesting to note that this intense Cotton effect was not observed with the *cis* isomers 114, 118 and 119. The CD Cotton effects for 118 and 119 were minimums at 216 nm with values of $[\theta]_{216}$ = -2,900 and

$[\theta]_{216}$ = -2,900, respectively. These CD spectral results support the assignments[175] by Joullié and co-workers of 116 as an L-α-amino acid and 117, 118 and 119 as D-α-amino acids. In addition, a comparison of the physical and spectral properties of 118 (Joullié) and 114 (this work) revealed that they are similar. The optical rotations were +6.9° for 118 and -8° for 114 and the CD Cotton effects were $[\theta]$ = -2,900 for 118 and $[\theta]$ = +2,200 for 114. This data indicates that 118 and 114 are enantiomers and therefore the structure of 118 can be assigned 2(R)-amino-2-[2,5-dihydro-5(S)-methylfuran-2(S)-yl]ethanoic acid.

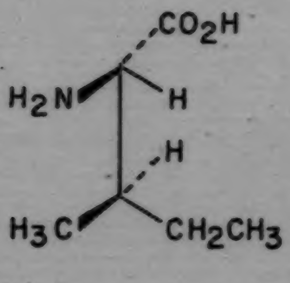
A similar inspection of the physical and PMR spectral data for 119 (Joullié) and 113 (this work) revealed that they are similar. We observed that the optical rotation of 119 (Joullie) had a value of $[\alpha]_D$ = +35°. It was already determined that 114 had a rotation of $[\alpha]_D$ = -8°. Assuming that 113 (this work) and 119 (Joullie) are identical and our synthetic product 113 contained approximately 18% of 114, the optical rotation for this mixture was calculated as $[\alpha]_D$ = +27°. This is in good agreement with the observed rotation $[\alpha]_D$ = +21° for the mixture of 113 (82%) and 114 (18%). The CD spectrum of 113 (containing 18% of 114) was similar to that observed for 119 and had a value of $[\theta]_{216}$ = -1,700. Therefore it is proposed that the structure of 119 is assigned 2(*R*)-amino-2-[2,5-dihydro-5(*R*)-methylfuran-2(*R*)-yl]ethanoic acid.

Considering all of the preceding information we propose that the originally suggested structure (**114**) for furanomycin (which we prepared in the present work by a classical stereochemically defined approach) is not identical to the natural antibiotic. The synthetic studies, empirical ^{1}H NMR correlations made by Joullié and the CD data from this laboratory are in agreement with the assignment of structure **116** to the antibiotic furanomycin. Further definitive proof would require a single crystal X-ray determination.

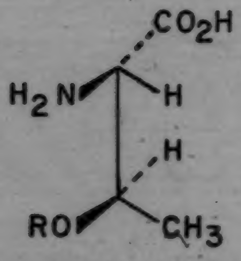
In conclusion, a note of interest may be made concerning the relationship between the biological activity and structure of furanomycin as a metabolic antagonist. As previously mentioned in the introduction, furanomycin in some respects resembles the polyoxins (**7**) and the recently synthesized,[176] 2(*S*)-amino-2-[3-chloro-4,5-dihydroisoxazol-5(*S*)-yl]-ethanoic acid (**15**). One apparently unrecognized structural feature distinguishing these inhibitors is the configuration at the β-position. Surprisingly little mention is made in the literature of the stereochemical requirement of α-amino acids other than at the α position. Those reports that have appeared on *L*-isoleucine, *L*-threonine, *L*-phenylserine and L-allo-isoleucine,[177,178] noted that the configuration at the β-position is important. For example,[177] it was found that the rate of L-amino acid oxidase with L-threonine and L-isoleucine was faster for a β-L configuration than for the corresponding β-D diastereomer. In a similar manner, the rate of D-amino acid oxidase with D-isoleucine and D-threonine was found to be faster for the β-D than the β-L configuration. Chemical[179] and X-ray[180] analyses have shown that the configuration at the β carbon of the naturally occurring diastereomer of L-isoleucine (120) is (S). Similarly, it has been established[181,182] that the configurations of L-threonine (121) and L-allothreonine (122) correspond to those of L-isoleucine (120) and L-alloisoleucine (123), respectively. Also, studies with L-O-methylthreonine (124) and its diastereomer L-O-methylallothreonine (125) indicated that the former is a competitive inhibitor of L-isoleucine incorporation whereas the latter is not. This reflects the enzyme-substrate specificity involved in the utilization of L-isoleucine. It is tempting to speculate that the specificity of furanomycin as an L-isoleucine antagonist could be mimicked by other L-amino acid derivatives with substituents and configuration at the β-carbon resembling those of threonine or L-O-methylthreonine. The crystal



120

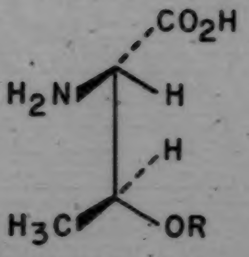


123



121 R=H

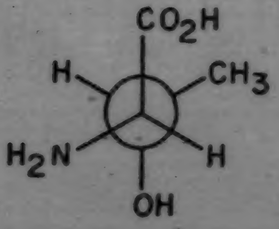
124 R=CH_3



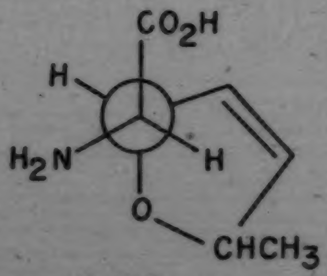
122 R=H

125 R=CH_3

structure of L-threonine has been established and the solid state conformation is as indicated in 126. It is possible that furanomycin would assume an analogous

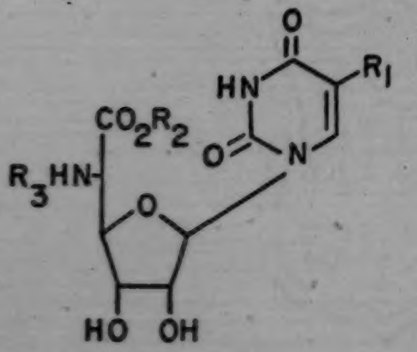


126



127

conformation as shown in 127. It may also be noted that the configuration at the β-carbons for the antibiotics polyoxin (7) and 2(S)-amino-2-[3-chloro-4,5-dihydroisoazol-5(S)-yl] ethanoic acid (15) stereochemically resemble those for L-allothreonine (122) or L-O-methylallothreonine (125) the diastereomers of L-threonine and L-O-methylthreonine.

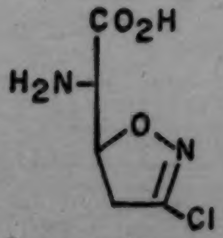


R_1 = CH_2OH, CO_2H, CH_3

R_2 = 3-Ethylidene-L-azetidine-2-carboxylic acid

R_3 = 5-O-carbamoyl-2-amino-2-deoxy-L-xylonic acid or 3-deoxy derivative

7



15

SUMMARY

A synthetic route to 2(S)-amino-2-[2,5-dihydro-5(R)-methylfuran-2(R)-yl]ethanoic acid (cis diastereomer of furanocyin) (114) has been devised starting with 1,3-diphenyl-2-(5-O-benzoyl-2,3-O-isopropylidene-β-D-ribofuranosyl)imidazolidine (44). The 5-O-benzoyl group was converted to the 5-O-benzyl group by deprotection with methanolic sodium hydroxide followed by reaction with benzyl bromide and sodium hydride in dimethylformamide. Hydrolysis of the imidazolidine protecting group of 90 with p-toluenesulfonic acid gave the free aldehyde which was treated directly with sodium cyanide and potassium carbonate followed by hydrogen peroxide. This modified Strecker-type synthesis led to the isolation of 3,6-anhydro-7-O-benzyl-4,5-O-isopropylidene-D-glycero-D-(allo and altro)-heptoamides (91 and 92) which were separated by fractional crystallization. In the subsequent series of reactions each isomer was treated separately. The 2-hydroxy function was protected with acetic anhydride in pyridine. Conversion to the 7-deoxy derivative (101 and 102) was accomplished by debenzylation with hydrogen over Pd-C followed by mesylation, displacement with sodium iodide and reduction of the 7-iodo derivation with hydrogen over Pd-C. The 2-O-acetyl function was removed with methanolic ammonia. Reaction of this α-hydroxy amide

derivative with mesyl chloride followed by displacement with lithium azide gave a key intermediate 3,6-anhydro-2-azido-2,7-dideoxy-4,5-O-isopropylidene-D-glycero-D-(allo and altro)-heptonamide (107 and 108). Concomitant solvolysis of the amide and isopropylidene functions was achieved using ANGC(H^+) resin in methanol. The resulting α-azido ester was treated with bis-imidazole thiocarbonate to give the 4,5-O-thiocarbonato intermediate (111 or 112). Reductive elimination of the thiocarbonate function with trimethylphosphite (Corey-Winter procedure) gave accompanying reduction of the azide function. Hydrolysis of this intermediate with 1N sodium hydroxide gave the desired products, 2-(R and S)-amino-2-[2,5-dihydro-5(R)-methylfuran-2(R)-yl]-ethanoic acid (113 and 114).

A recent report by M. M. Joullié and co-workers suggested that the structure of the antibiotic furanomycin be revised to 2(S)-amino-2-[2,5-dihydro-5(S)-methylfuran-2(R)-yl]ethanoic acid (trans diastereomer of our synthetic product, 116). These workers also prepared 2(R)-amino-2-[2,5-dihydro-5(S)-methylfuran-2(R)-yl]ethanoic acid (117) and the diastereomeric 2(R)-amino-2-[2,5-dihydro-5(R and S)-methylfuran-2-(R and S)-yl]ethanoic acids (118 and 119). The configurations at C_3 and C_6 of the latter compounds were unknown. In private communication with Professor

Joullié we determined that the CD Cotton effects were in agreement with their original assignments of configuration at C-2 for the α-amino acids. Furthermore it was found that 2(*R*)-amino-2-[2,5-dihydro-5(*S*)-methylfuran-2(*S*)-yl]ethanoic acid (**118**) prepared by Joullié and coworkers was the enantiomer of our *cis* L-α-amino acid product, and their 2(*R*)-amino-2-[2,5-dihydro-5(*R*)-methylfuran-2(*R*)-yl]ethanoic acid (**119**) was identical to our *cis* D-α-amino acid, on comparison of their physical and spectral properties.

It was concluded that the independent synthetic studies, empirical ^{1}H NMR correlations made by Joullié and the CD data from this laboratory are in agreement with the assignment of natural furanomycin as 2(*S*)-amino-2-[2,5-dihydro-5(*S*)-methylfuran-2(*R*)-yl]ethanoic acid and not 2(*S*)-amino-2-[2,5-dihydro-5(*R*)-methylfuran-2(*R*)-yl]ethanoic acid as proposed originally.

EXPERIMENTAL

A. General Procedures

Melting points are uncorrected and were taken on a Reichert microstage apparatus. Ultraviolet spectra were recorded on a Cary 15 spectrometer in methanol. Infrared spectra were recorded on a Nicolet 7199 FT(IR) spectrometer, in chloroform solution, as a neat film or in KBr pellet. The CD and ORD spectra were run on a Jasco ORD-UV-5 (CD SS-20) spectrophotopolarimeter in H_2O or HCl solutions. Optical rotations were determined with a Perkin Elmer 241 polarimeter. Proton NMR spectra were recorded on a Varian HA-100 instrument normally in $CDCl_3$ unless specified otherwise. The 200 and 400 MHz spectra were recorded in D_2O on a Bruker WH 200 and Bruker WH 400 instrument, respectively. The ^{13}C NMR spectra were run on a Bruker HFX90 (Nicolet 1080) instrument in D_2O. Mass spectra were obtained by the mass spectroscopy laboratory of this department on an AEI MS-50 (70 e/v) instrument using direct probe sample introduction from 100-250°C. Chemical ionization mass spectroscopy data was obtained using the AEI MS-12 (NH_3) instrument. All peaks quoted gave satisfactory agreement in mass measurements with the structures assigned. Elemental analyses were determined by the microanalytical laboratory of this department.

All solvents were distilled prior to use. Skelly "B" was distilled and that fraction boiling at 63-65°C was recovered. Purifications of solvents and reagents were accomplished according to those described in "Purification of Laboratory Chemicals", D. D. Perrin, W. L. F. Armarego and D. R. Perrin, Pergamon Press of Canada Ltd., 6 Adelaide St. East, Toronto, Ontario, 1966. Reactions were protected from moisture using a drying tube filled with calcium sulfate unless the reaction was performed under nitrogen. Solutions were dried with anhydrous sodium sulfate prior to concentration. Evaporations were carried out using a Buchi rotary evaporator equipped with a dry ice condensor using the water aspirator or oil pump vacuum. Hydrogenations were performed over 5% palladium on charcoal catalysts obtained from Eastman Kodak Co., Rochester, New York or from Apache Chemicals Inc., Seward, Illinois. For hydrogenation of the tri-O-benzyl derivatives, this catalyst was activated by washing with 1N HCl followed by H_2O. The catalyst was then dried and kept under vacuum. Raney Nickel (#28) was purchased from W. R. Grace and Co., South Pittsburg, Tennessee.

Thin layer chromatography (TLC) was performed on Eastman chromatagram sheets (silica gel #13181 indicator #6060) when monitoring with UV light (254 nm). Glass plates (75 x 25 mm, coated with silica gel prepared in a chloroform slurry) were used for detection by spraying with a 5% H_2SO_4-EtOH solution and heating the plates to 100-200°C. Silica gel column chromatography was performed using J. T. Baker #5-3405 (60-200 mesh) silica gel. Ion exchange chromatography and amide hydrolysis with acid resin was effected using ANGC(H^+)-244 resin from J. T. Baker Chem. Co. The systems used for silica gel chromatography were solvent A: Skelly "B"-ethyl acetate (5:1), solvent B: Skelly "B"-ethyl acetate (1:1), solvent C: Skelly "B"-chloroform (1:1), solvent D: Skelly "B"-ether (1:1), solvent E: Skelly "B"-ether (1:4), solvent F: Skelly "B"-ether (4:1), solvent G: chloroform-ethyl acetate (1:1), solvent H: Skelly "B"-ethyl acetate (1:2), solvent K: Skelly "B"-ethyl acetate (3:1). Paper chromatography was performed on Whatman #2 chroma sheets. The solvents used for ascending chromatography were solvent M: n-propanol-water (7:3) and solvent N: n-butanol-acetic acid-water (4:1:6 upper phase). The products were detected by ninhydrin spray using color development at room temperature.

B. Syntheses

Reaction of diethyl malonate, diethyl acetamidomalonate and diethyl nitromalonate with 5-*O*-trityl-2,3-*O*-isopropylidene-β-*D*-ribofuranosyl choride, to give 37 - 40

The diethyl malonate (2 mmol) in dimethoxyethane (5 ml) was added to a stirred suspension of sodium hydride (96 mg, 50% oil suspension, 2 mmol) in dimethoxy ethane (5 ml) under nitrogen at 0°C. After 0.5 h at room temperature, the mixture was treated with sodium iodide (300 mg, 2 mmol) and chloro sugar 36 (900 mg, 2 mmol) and stirred at reflux for 2 h. The mixture was cooled and poured into ether (50 ml) and saturated aqueous ammonium chloride (100 ml). The organic layer was washed with saturated brine (3 x 25 ml) dried and evaporated to a syrup. The residue was purified by chromatography on silica (20 g, 2.2 x 18 cm). Elution with solvent A gave the desired product 37, 38 (85%), 39 (~45%), 40 (~45%): IR (film) (39) 1745 cm^{-1} ($CO_2C_2H_5$); (40) 1680 cm^{-1} ($NHCOCH_3$), 1730 cm^{-1} ($CO_2C_2H_5$). NMR ($CDCl_3$) δ 1.00 - 1.50 (m, 12, $CO_2C_2H_5$ and $C(CH_3)_2$), 3.00 - 5.00 (m, sugar), 7.00 - 7.50 (m, 15, C_6H_5); for (39) δ 6.00 (d, J_{3-4} = 5 Hz, 1, H_3), (40) 5.40 (d, J_{3-4} = 8 Hz, 1, H_3).

3,6-Anhydro-4,5,7-tri-*O*-benzoyl-D-glycero-D-(allo and altro)-heptononitrile (42)

A stirred solution of the protected ribofuranosyl imidazolidine (23, R = Bz) (1.33 g, 2 mmol) in methylene chloride (40 ml) at room temperature was treated with p-toluenesulfonic acid (1.14 g, 6 mmol) in acetone (10 ml). After 1 h the solution was diluted with methylene chloride (40 ml) and filtered. The filtrate was treated with sodium bicarbonate (2 g). This mixture was re-filtered and evaporated to a syrup. The residue was dissolved in p-dioxane (40 ml), cooled to 10°C and treated with sodium cyanide (2 g) in water (20 ml). After 0.5 h at room temperature the mixture was diluted with saturated brine (20 ml) and extracted with ethyl acetate (3 x 25 ml). The combined organic layers were washed with saturated brine (3 x 10 ml) dried and evaporated. The residue was chromatographed on silica (25 g, 2 x 14 cm). Elution with solvent B gave 910 mg (91%) of 42: IR (film) 1725 cm^{-1} (benzoate), 3450 cm^{-1} (OH); NMR ($CDCl_3$) δ 4.2 - 4.7 (bs, 1, OH), 4.4 - 4.6 (m, 1, H_3), 4.5 - 4.8 (m, 3, H_5 and H_6,$H_{6'}$), 4.8 - 4.9 (m, 1, H_2), 5.6 - 5.9 (m, 2, H_5 and H_4), 7.0 - 8.1 (m, 15, C_6H_5).

Anal. Calcd for $C_{28}H_{23}O_8N$: C, 67.06; H, 4.59; N, 2.79; O, 25.54. Found: C, 66.04; H, 4.67; N, 2.66; O, 25.54.

3,6-Anhydro-2-O-acetyl-4,5,7-tri-O-benzoyl-D-glycero-D-(allo and altro)-heptononitrile (43)

A solution of the α-hydroxy nitrile (42) (910 mg, 1.8 mmol) was dissolved in pyridine (25 ml) at 0°C and treated with acetic anhydride (1 ml). After 16 h at 0°C the solution was diluted with ice water (50 ml) and extracted with chloroform (3 x 25 ml). The combined organic layers were washed with 1N hydrochloric acid, saturated sodium bicarbonate and saturated brine. The solution was dried and evaporated to give 830 mg (76%) of 43 as a syrup. One isomer was fractionally crystallized from chloroform-Skelly "B" (20%): mp 148 - 150°C; IR (KBr) 1725 cm^{-1} (benzoate), 1760 cm^{-1} (acetate); NMR ($CDCl_3$) δ 2.0 (s, 3, $COCH_3$), 4.5 - 4.9 (m, 4, H_3, H_6, H_7, $H_{7'}$), 5.6 - 5.9 (m, 3, H_2, J_4, H_5), 7.1 - 8.2 (m, 15, C_6H_5).

Anal. Calcd for $C_{30}H_{25}O_9N$: C, 66.30; H, 4.60; N, 2.58. Found: C, 66.60; H, 4.66; N, 2.48.

2,5-Anhydro-3,4-O-isopropylidene-D-allose (27)

A stirred solution of the ribofuranosyl imidazolidine (45) (396 mg, 1 mmol) in methylene chloride (15 ml) at room temperature was treated with p-toluenesulfonic acid monohydrate (570 mg, 7 mmol) in acetone (1 ml). After 15 min the dense white mixture was diluted with ether (25 ml) and filtered through celite. The filtrate was concentrated to a white gum and dissolved in ethyl acetate (25 ml). This solution was washed with a small volume of saturated brine (5 ml). The aqueous layer was extracted with ethyl acetate (3 x 5 ml). The combined organic layers were dried and evaporated to a white solid (210 mg, quantitative). This solid was crystallized from chloroform and Skelly "B" to give 150 mg (75%) of 27: mp 168 - 170°C; Lit.[81] mp 185 - 186°C; NMR [$(CD_3)_2CO$] δ 1.30 and 1.38 (s+s, 3+3, $C(CH_3)_2$), 2.85 (m, 1, OH), 3.20 - 3.65 (m, 1, H), 3.80 - 4.10 (m, 1, H), 4.61 - 4.85 (m, 3, H); MS m/e 202.0843 (1.35, M^+, calcd for $C_9H_{14}O_5$: 202.0841), 187.0608 (100, M^+-CH_3), 185.0815 (5.44, M^+-OH), 173.0813 (6.13, $M^+-OH-CH_3$).

Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.93; O, 39.60. Found: C, 53.24; H, 7.00; O, 39.69.

3,6-Anhydro-2,N-benzylamino-2-deoxy-4,5-O-isopropylidene-D-glycero-D-(allo and altro)-heptononitrile (47) and heptonamide (48)

Sodium cyanide (249 mg) in water (25 ml) was added to a solution of hemiacetal (27) (202 mg, 1 mmol) in water (9 ml). After 15 min at room temperature, a solution of benzylamine hydrochloride (149 mg) in water (2.5 ml) was added. The solution was heated at 80°C for forty minutes, cooled and extracted with chloroform (3 x 25 ml). The combined organic layers were dried and evaporated to give 210 mg (65%) of 47: NMR ($CDCl_3$) δ 1.32 and 1.48 (s+s, 3+3, $C(CH_3)_2$), 3.0 (bs, 2, OH and $N\underline{H}C_7H_7$), 3.5 - 4.9 (m, 9, sugar and $\underline{CH}_2C_6H_5$), 7.3 (m, 5, C_6H_5); MS m/e 291 (M^+-HCN), 276 (M^+-HCN-CH_3), 195 (M^+-$C_9H_8N_2$).

This residue was dissolved in p-dioxane (5 ml) cooled to 10°C and treated with potassium carbonate (100 mg) in water (2.5 ml), followed by 30% H_2O_2 (2.5 ml). The mixture was stirred at room temperature for 2 h and extracted with methylene chloride (3 x 10 ml). The combined organic layers were washed with water (2 x 10 ml) dried and evaporated. The residue was purified by chromatography on silica (10 g, 1.8 x 13 cm). Elution with ethyl acetate followed by ethyl acetate-ethanol (9:1) gave 180 mg (53%) of 48 as a syrup: NMR ($CDCl_3$) δ 1.32 and 1.92 (s+s, 3+3, $C(CH_3)_2$), 3.0 (bs, 2, OH and $N\underline{H}C_7H_7$), 3.2 - 4.7 (m, 9, sugar and $\underline{CH}_2C_6H_5$), 6.05 and 7.0 (bs, 2, $CONH_2$), 7.3 (s, 5, C_6H_5); MS m/e 321 (M^+-CH_3), 292 (M^+-$CONH_2$), 230 (M^+-NHC_7H_7).

Methyl 2,3,5-tri-O-methanesulfonyl-β-D-ribofuranoside (49)

Methanesulfonyl chloride (15 g, 10 ml, 120 mmol) was added dropwise to a stirred solution of methyl β-D-ribofuranoside[162] (5 g, 30 mmol) in pyridine (75 ml) at 0°C. After 30 min at 0°C the solution was heated at 40°C for 45 min and poured into a mixture of ice water (500 ml) and methylene chloride (200 ml). The aqueous layer was extracted with methylene chloride (3 x 100 ml). The combined organic layers were washed with saturated sodium bicarbonate (3 x 50 ml), saturated brine (3 x 25 ml), dried and evaporated to a solid. This residue was crystallized from chloroform-ethanol to give 10.7 g (88%) of 49: mp 140 - 141°C $[\alpha]^{23}_{D}$ - 4° (c 0.2, $CHCl_3$); NMR ($DMSO-d_6$) δ 3.20 (s, 3, OCH_3), 3.25 - 3.30 (3 singlets, 9, SO_3CH_3), 4.35 (m, 3, H_4 and $H_{5,5'}$), 5.05 - 5.30 (m, 2, H_2 and H_3), 5.12 (s, 1, H_1); MS m/e 319 ($M^+-SO_2CH_3$), 289 ($M^+-SO_2CH_3$ - OCH_3), 240 ($M^+-2.SO_2CH_3$).

Anal. Calcd for $C_9H_{18}S_3O_{11}$: C, 27.14; H, 4.52; S, 24.12. Found: C, 27.14; H, 4.46; S, 24.10.

Methyl 5-deoxy-5-iodo-2,3-di-O-methanesulfonyl-β-D-ribofuranoside (51)

A solution of the tri-mesyl derivative (49) (1.2 g, 3 mmol) in dimethylformamide (10 ml) was treated with sodium iodide (450 mg, 3 mmol) and heated at 150°C for 30 min. The mixture was cooled, diluted with chloroform (20 ml) and filtered. The solid was washed with chloroform (30 ml). The combined filtrates were washed with 5% aqueous sodium bisulfite solution (3 x 10 ml), saturated brine (3 x 10 ml), dried and evaporated to a solid. This residue was crystallized from MeOH to give 1.25 g (91%) of 51: mp 108 - 109°C; $[\alpha]_D^{23}$ - 4° (c 0.2, $CHCl_3$); NMR ($CDCl_3$) δ 3.14, 3.17 (s+s, 3+3, SO_3CH_3), 3.45 (s, 3, OCH_3), 3.30 - 3.45 (m, 2, $H_{5,5'}$), 4.25 (m, 1, H_4), 5.00, 5.05 (m, 2, H_2 and H_3), 5.10 (s, 1, H_1); MS m/e 398.9088 (0.48, M^+-OCH_3, calcd for $C_7H_{12}O_7S_2I$: 398.9106), 350.9406 (3.94, M^+-SO_2CH_3).

Anal. Calcd for $C_8H_{15}S_2O_8I$: C, 22.32; H, 3.49; S, 14.88; I, 29.53. Found: C, 22.36; H, 3.46; S, 15.00; I, 29.52.

Methyl 5-deoxy-2,3-di-O-methanesulfonyl-β-D-ribofuranoside (53)

A solution of the iodo derivative (51) (430 mg, 1 mmol), triethylamine (150 mg) and a chip of dry ice in ethyl acetate-ethanol (2:1, 10 ml) was hydrogenated at atmospheric pressure over 5% Pd-C (50 mg). After 5 h the mixture was filtered and evaporated. The residue was dissolved in chloroform (50 ml), washed with 5% sodium bisulfite (3 x 10 ml), saturated brine

(3 x 10 ml), dried and evaporated to give 300 mg (98%) of 53 as a syrup. This product was homogeneous by TLC (EtOAc, R_f = 0.8): NMR ($CDCl_3$) δ 1.45 (d, J_{5-4} = 6 Hz, 3, CH_3), 3.11, 3.13 (s+s, 3+3, SO_3CH_3), 3.40 (s, 3, OCH_3), 4.28 (q, J_{4-5} = 6 Hz, J_{4-3} = 6 Hz, 1, H_4), 4.80 - 5.10 (m, 3, H_1, H_2 and H_3).

Anal. Calcd for $C_8H_{16}S_2O_8$: C, 31.58; H, 5.26; S, 21.05. Found: C, 31.43; H, 5.24; S, 20.70.

Methyl 5-deoxy-5-iodo-2,3-di-O-p-toluenesulfonyl-β-D-ribofuranoside (52)

A solution of the 2,3,5-tri-O-tosyl derivative[153] (50) (626 mg, 1 mmol) and sodium iodide (150 mg, 1 mmol) in dimethylformamide (5 ml) was heated at 150°C for 30 min, cooled and poured into a mixture of 5% sodium bisulfite and ether (50 ml). The organic layer was washed with saturated brine (3 x 20 ml), dried and evaporated to give 590 mg (quantitative) of 52: NMR (90 MHz) ($CDCl_3$) δ 2.45 (s, 6, $SO_3C_6H_4CH_3$), 2.90 - 3.35 (m, 2, $H_{5,5'}$), 3.35 (s, 3, OCH_3), 4.10 (m, 1, H_4), 4.60 - 4.80 (m, 2, H_2 and H_3), 4.98 (s, 1, H_1), 7.20 - 7.90 (m, 8, C_6H_4).

Methyl 5-deoxy-2,3-di-O-p-toluenesulfonyl-β-D-ribofuranoside (54)

A solution of the iodo derivative (52) (200 mg, 0.34 mmol), triethylamine (250 mg) and a chip of dry ice in ethanol (10 ml) was hydrogenated over 5% Pd-C at atmospheric pressure. After 4 h the mixture was filtered and evaporated. The residue was dissolved in chloroform (25 ml) and washed with 5% sodium bisulfite (2 x 5 ml), saturated brine (2 x 5 ml), dried and evaporated to give 135 mg (85%) of 54 as a syrup: NMR (90 MHz) ($CDCl_3$) δ 1.10 (d, J_{5-4} = 7 Hz, 3, CH_3), 2.45 (s, 6, $SO_3C_6H_4CH_3$), 3.25 (s, 3, OCH_3), 4.15 (q, J_{4-5} = 7 Hz, J_{4-3} = 7 Hz, 1, H_4), 4.50 - 4.80 (m, 2, H_2 and H_3), 4.90 (s, 1, H_1), 7.25 - 7.90 (m, 8, C_6H_4).

1,3-Diphenyl-2-(2,3-O-isopropylidene-β-D-ribofuranosyl)-imidazolidine (45)

A solution of the 5-O-benzoyl imidazolidine derivative (44) (10 g, 10 mmol) (prepared by Moffatt and co-workers [56]) in chloroform (150 ml) was added to a stirred solution of 0.1N sodium hydroxide in methanol (150 ml) at room temperature. After 2.5 h the solution was poured into chloroform (200 ml) and saturated ammonium chloride (200 ml). The aqueous layer was extracted with chloroform (3 x 25 ml). The combined organic layers were washed with saturated brine (3 x 20 ml) dried and evaporated to a white solid. This residue was dissolved in hot methanol (150 ml) and allowed to crystallize at room temperature. The product was filtered to give 7.5 g (95%) of 45: mp 170 - 171°C; $[\alpha]_D^{23}$ - 50° (c 0.2, $CHCl_3$); UV (MeOH) max 253 nm (ε 34,700), 293 nm (ε 4400); NMR ($CDCl_3$) δ 1.26 and 1.35 (s+s, 3+3, $C(CH_3)_3$), 2.2 (bs, 1, OH), 3.3 - 4.7 (m, 10, sugar and CH_2CH_2), 5.65 (s, 1, H_1), 6.7 - 7.3 (m, 10, C_6H_5); MS m/e 398.2159 (1.34, M^{+}+2), 397.2124 (4.07, M^{+}+1, calcd for $C_{23}H_{29}N_2O_4$: 397.2127), 396.2029 (1.21, M^{+}), 395.1971 (2.38, M^{+}-1), 382.1857 (0.94, M^{+}+1-CH_3), 381. 1820 (2.99, M^{+}-CH_3).

Anal. Calcd for $C_{23}H_{28}N_2O_4$: C, 69.69; H, 7.07; N, 7.07. Found: C, 69.53; H, 7.00; N, 7.09.

1,3-Diphenyl-2-(5-O-mesyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-imidazolidine (55b)

Methanesulfonyl chloride (170 mg, 1.5 mmol) in methylene chloride (1 ml) was added to a solution of the imidazolidine sugar (45) (396 mg, 1 mmol) in pyridine (4 ml) at 0°C. After 4 h at 0°C the solution was poured into saturated sodium bicarbonate (20 ml) and methylene chloride (30 ml). The organic layer was washed with water (2 x 10 ml), dried and evaporated to give 450 mg of a white solid. This residue was crystallized from methanol to give 400 mg (84%) of 55a: mp ~130° decomposition; $[\alpha]_D^{23}$ - 41° (c 0.1, $CHCl_3$); UV (MeOH) max 254 nm (ε 33,400), 292 nm (ε 5000); NMR ($CDCl_3$) δ 1.25 and 1.35 (s+s, 3+3, $C(CH_3)_2$),

2.80 (s, 3, SO_2CH_3), 3.4 - 4.8 (m, 10, sugar, CH_2CH_2), 5.60 (d, $\underline{J}_{1-2}$ = 2 Hz, 1, H_1), 6.6 - 7.4 (m, 10, C_6H_5); MS m/e 475.1846 (0.20, M^++1), 474.1804 (0.46, M^+, calcd for $C_{24}H_{30}N_2SO_6$: 474.1848), 473.1743 (0.44, M^+-1), 379.1975 (1.50, M^+-OMs), 378.1949 (6.01, M^+-HOMs), 368.1192 (0.42, M^+-CH_3-NC_6H_5).

Anal. Calcd for $C_{24}H_{30}N_2SO_6$: C, 60.76; H, 6.33; N, 5.91; S, 6.75. Found: C, 60.61; H, 6.40; N, 5.63; S, 6.80.

1,3-Diphenyl-2-(5-chloro-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranosyl)imidazolidine (55c)

A solution of the imidazolidine sugar (45) (1.18 g, 3 mmol) in pyridine (30 ml) under nitrogen was cooled to 0°C and treated with triphenylphosphine (1.57 g, 6 mmol) and carbon tetrachloride (0.57 ml, 6 mmol). The solution was allowed to stand at room temperature for 24 h, treated with methanol (5 ml) and evaporated to a gummy residue. The residue was chromatographed on silica (10 g, 1.8 x 11 cm). Elution with solvent C gave a white solid after evaporation of the solvent. This residue was crystallized from methanol to give 1.1 g (88%) of 55c: mp 126 - 127°C; $[\alpha]^{23}_{D}$ - 30° (c 0.11, $CHCl_3$); UV (MeOH) max 253 nm (ε 31,200), shoulder, 293 nm (ε 4,100); NMR ($CDCl_3$) δ 1.27 and 1.41 (s+s, 3+3, $C(CH_3)_2$), 3.40 - 3.90 (m, 4,

CH_2CH_2), 4.07 (q, $\underline{J}_{5-6,6'}$ = 5 Hz, 1, H_5), 4.40 - 4.50 (m, 2, H_2 and H_4), 4.68 (d of d, $\underline{J}$ = 5 Hz, $\underline{J}$ = 6.5 Hz, 1, H_3), 5.59 (d, $\underline{J}_{1-2}$ = 1.52 Hz, 1, H_1), 6.50 - 7.40 (m, 10, C_6H_5); MS m/e 416.1756 (0.55, M^++2), 415.1786 (1.22, M^++1, calcd for $C_{23}H_{28}N_2O_3Cl$: 415.1788), 414.1746 (1.00, M^+), 413.1675 (0.62, M^+-1), 401, 1456 (0.55, M^++2 - CH_3), 399.1464 (1.16, M^+-CH_3).

Anal. Calcd for $C_{23}H_{27}N_2O_3Cl$: C, 66.51; H, 6.75; N, 6.75; Cl, 8.43. Found: C, 66.35; H, 6.64; N, 6.50; Cl, 8.68.

1,3-Diphenyl-2-(5-deoxy-2,3-O-isopropylidene-β-D-ribofuranosyl)imidazolidine (55d)

A solution of the 5-chloro sugar imidazolidine (55c) (1.25 g, 3 mmol) in benzene (30 ml) was refluxed with tri-n-butyltin hydride (6 ml of 1M solution, 6 mmol) and azobisisobutyronitrile (50 mg) under nitrogen for 12 h. The solution was evaporated to a syrup and chromatographed on silica (20 g, 2.2 x 18 cm). Elution with Skelly "B" followed by solvent D gave a white solid. This was crystallized from methanol to give 1.03 g (90%) of 55d: mp 113 - 114°C; $[\alpha]_D^{23}$ - 39° ($\underline{c}$ 0.1, $CHCl_3$); UV (MeOH) max 254 nm (ε 34,600), shoulder 292 nm (ε 5,100); NMR ($CDCl_3$) δ 1.20 (d, $\underline{J}_{5-6}$ = 7 Hz, 3, CH_3), 1.23 and 1.37 (s+s, 3+3, $C(CH_3)_2$), 3.50 - 4.70 (m, 8, sugar CH_2CH_2), 5.51 (d, $\underline{J}_{1-2}$ = 1.9

Hz, 1, H_1), 6.60 - 7.40 (m, 10, C_6H_5); MS m/e 380.2090 (0.12, M^+, calcd for $C_{23}H_{28}N_2O_3$: 380.2065), 379.2018 (0.17, M^+-1), 365.1860 (0.28, M^+-CH_3).

Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.63; H, 7.37; N, 7.37; O, 12.63. Found: C, 72.54; H, 7.58; N, 7.09; O, 12.79.

5-O-Benzoyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl-nitrile (58)

A mixture of the ribofuranosyl nitrile (56) (5.26 mg, 2 mmol) and sodium iodide (600 mg) in acetonitrile (10 ml) was treated with α-acetoxyisobutyryl-chloride (700 mg) at room temperature. After 1.5 h the mixture was diluted with chloroform (40 ml), washed with saturated sodium bicarbonate (2 x 20 ml), 5% sodium bisulfite (2 x 20 ml), dried and evaporated to give 900 mg of a syrup. This was dissolved in acetic acid (30 ml) and water (10 ml) cooled to -20°C and treated with freshly prepared Zn-Cu couple. After stirring for 1 h the reaction was filtered, the solid washed with 50% acetic acid (20 ml) and the filtrates extracted with chloroform (3 x 10 ml). The combined organic phase was washed with saturated sodium bicarbonate, water (2 x 10 ml), dried and evaporated to give 540 mg of a syrup. TLC revealed this to be a mixture of products. Preparative TLC gave the desired product 58 (~60%): NMR ($CDCl_3$) (90 MHz) δ 4.5 (dd, $J_{6-6'}$ ≈ 13 Hz, $J_{6,5}$ ≈ 3 Hz, 2, H_6 and $H_{6'}$), 5.2 (m, 1, H_5), 5.5 (m, J_{2-5} ≈ 2 Hz, 1, H_2), 5.96 and 6.16 (m, J_{3-4} ≈ 6 Hz, 2, H_3 and H_4), 7.2 - 8.2 (m, 5, C_6H_5).

Methyl 5-O-trityl-β-D-ribofuranoside (59)

A solution of methyl β-D-ribofuranoside[162] (1.64 g, 10 mmol) in pyridine (25 ml) was treated with trityl chloride (3.3 g, 12 mmol) at 0°C and then allowed to stand at room temperature for 48 h. The solution was diluted with chloroform (100 ml), washed with saturated brine (3 x 25 ml), dried and evaporated to a syrup. This residue was purified by chromatography on silica (50 g, 3 x 20 cm). Elution with solvent D followed by ether gave 3.78 (93%) of 59 as a clear viscous syrup: $[\alpha]^{23}_{D}$ - 28° (*c* 1.8, $CHCl_3$); Lit.[163], $[\alpha]^{23}_{D}$ - 7.5° (*c* 1.9, $CHCl_3$); NMR ($CDCl_3$) δ 2.50 - 3.90 (bs, 2, OH), 3.25 (s, 3, OCH_3), 3.10 - 3.40 (m, 2, $H_{5,5'}$), 3.90 - 4.30 (m, 3, $H_{2,3,4}$), 3.95 (d of d, J_{2-1} = 0.5 Hz, J_{2-3} = 5 Hz, 1, H_2), 4.82 (d, J_{1-2} = 0.5 Hz, 1, H_1), 7.10 - 7.60 (m, 15, C_6H_5); MS m/e 374.1518 (1.40, M^+-$HOCH_3$, calcd for $C_{24}H_{22}O_4$: 374.1518).

Methyl 2,3-*O*-thiocarbonato-5-*O*-trityl-β-*D*-ribofuranoside (60)

A solution of the 5-*O*-trityl derivative (59) (2.05 g, 5 mmol) and diimidazole thiocarbonate (1.3 g, 7.3 mmol) in dimethylformamide (25 ml) was heated at 90°C for 3 h, cooled, diluted with ether (50 ml) and poured into a solution of saturated sodium chloride (100 ml). The aqueous layer was extracted with ether (3 x 25 ml). The combined organic layers were dried and evaporated to give 2.13 g (91%) of a light yellow foam. This was dissolved in dimethylformamide (3 ml) and diluted with ethanol (20 ml). The resulting crystals were filtered to give 1.4 g (60%) of colorless needles (60): mp 125 - 126°C. An analytical sample was recrystallized from ethanol-chloroform: mp 132 - 133°C; $[\alpha]_D^{23}$ - 22° (*c* 1, $CHCl_3$); UV max (MeOH) 238 nm; NMR ($CDCl_3$) δ 3.12 (s, 3, OCH_3), 3.24 (m, $J_{5'-5''}$ = 10 Hz, 2, $H_{5'-5''}$), 4.51 (d of d, $J_{4-5'}$ = 6 Hz, $J_{4-5''}$ = 9 Hz, 1, H_4), 4.93 (d, $J_{2,3}$ = 7 Hz, 1, H_2), 5.02 (s, 1, H_1), 5.16 (d, J_{3-2} = 7 Hz, 1, H_3), 7.10 - 7.50 (m, 15, C_6H_5); MS m/e 488.1346 (2.7, M^+, calcd for $C_{26}H_{24}O_5S$: 488.1345).

Anal. Calcd for $C_{26}H_{24}O_5S$: C, 69.64; H, 5.36; S, 7.14. Found: C, 69.76; H, 5.60; S, 7.10.

Methyl 2,3-dideoxy-5-*O*-trityl-β-*D*-glycero-pent-2-enofuranoside (61)

A solution of the 2,3-*O*-thiocarbonate (60) (896 mg, 2 mmol) in trimethylphosphite (4 ml) was refluxed under nitrogen for 7 h. The mixture was cooled and concentrated to a syrup. This residue was chromatographed on silica (20 g, 2.2 x 18 cm). Elution with Skelly "B" - 1% pyridine followed by solvent D gave 670 mg (90%) of a white solid. This was dissolved in ether and diluted with pentane. The crystals that formed were collected to give 400 mg (54%) of pure 61: mp 87 - 88°C; Lit.[162] 82 - 83°C; $[\alpha]_D^{23}$ - 88° (*c* 1, $CHCl_3$). Lit.[162] $[\alpha]_D^{23}$ - 72° (*c* 1, $CHCl_3$); IR (KBr) 1625 cm^{-1} (C=C), 1590 cm^{-1}; NMR ($CDCl_3$) δ 3.00 - 3.40 (m, 2, $H_{5,5'}$), 3.40 (s, 3, OCH_3), 4.75 - 5.00 (m, 1, H_4), 5.70 - 5.90 (m, 2, $H_{2,3}$), 6.00 - 6.15 (m, 1, H_1), 7.10 - 7.60 (m, 15, C_5H_5).

1,3-Diphenyl-2-(5-*O*-dimethoxytrityl-β-*D*-ribofuranosyl) imidazolidine (63)

A solution of the imidazolidine sugar (62) (1.78 g, 5 mmol) in pyridine (25 ml) was heated at 70°C with dimethoxytrityl chloride (2.2 g, 6 mmol) for 45 min. The mixture was cooled, diluted with chloroform (100 ml), washed with saturated brine (3 x 20 ml), dried and evaporated to a syrup. This residue was purified by chromatography on silica (100 g, 4.5 x 18 cm). Elution with solvent D followed by solvent E gave 3.0 g (91%) of 63. TLC revealed the presence of a trace impurity (solvent B, R_f product = 0.2, R_f impurity =

0.26) in 63: $[\alpha]_D^{23}$ - 16° (c 0.1, $CHCl_3$); UV (MeOH) max 254 nm (ε 32,000), max 239 nm (ε 30,000), shoulder 278 nm (25,300); NMR ($CDCl_3$) δ 3.99 - 4.30 (m, 13, sugar, CH_2-CH_2), 3.75 (s, 6, OCH_3), 5.65 (bs, $\underline{J}_{1-2}$ ≈ 0.5 Hz, 1, H_1), 6.40 - 7.50 (m, 14, C_6H_5).

1,3-Diphenyl-2-(5-O-trityl-β-D-ribofuranosyl)imidazolidine (64)

A solution of the imidazolidine sugar (62) (712 mg, 2 mmol) and trityl bromide (969 mg, 3 mmol) in pyridine (10 ml) was heated at 60°C for 1 h. The course of the reaction was followed by TLC (EtOAc R_f. sm. 0.5, R_f. prod. 0.75). The reaction was cooled, diluted with chloroform (50 ml), washed with saturated sodium chloride (3 x 10 ml), dried and evaporated to a foam. This residue was purified by chromatography on silica (20 g, 2.2 x 10 cm). Elution with solvent D followed by ether gave 1.1 g (92%) of 64 as a white foam: $[\alpha]_D^{23}$ -17° (c 0.1, $CHCl_3$); UV (MeOH) max 256 nm (ε 31,800), shoulder 293 nm (ε 4,200); NMR ($CDCl_3$) δ 3.00 - 4.40 (m, 13, sugar) 5.65 (bs, $\underline{J}_{1-2}$ ≈ 0.5 Hz, 1, H_1), 6.50 - 7.70 (m, 15, C_6H_5): MS m/e 580.2728 (1.01, $M^+ - H_2O$, calcd for $C_{39}H_{36}N_2O_3$: 580.2726), 562.2601 (2.25, $M^+ - 2.H_2O$).

1,3-Diphenyl-2-(5-*O*-trityl-2,3-dideoxy-β-*D*-glycero-pent-2-enofuranosyl)imidazolidine (*66*)

A solution of the 5-*O*-trityl imidazolidine sugar (*64*) (598 mg, 1 mmol) in acetone (10 ml) was treated with diimidazole thiocarbonate (300 mg, 1.7 mmol) and left at room temperature. After 15 h the solution was evaporated to a syrup, and purified by filtering an ether solution of the residue over silica (5 g). Concentration of the ether filtrate gave 600 mg (93%) of solid *65*.

A solution of this thiocarbonate (640 mg, 1 mmol) in $P(OCH_3)_3$ (2 ml) was refluxed under nitrogen for 8 h, concentrated to a syrup and chromatographed on silica (10 g, 10 x 1.8 cm). Elution with Skelly "B" followed by solvent F gave 525 mg (93%) of solid *66*. Recrystallization of this material from ether-Skelly "B" gave 315 mg (56%) of pure product: mp 126 - 127°C; $[\alpha]^{23}_{D}$ - 35° (*c* 0.1, $CHCl_3$); UV (MeOH) max 256 nm (ε 31,400), shoulder 293 nm (ε 4,100); IR (KBr) cm^{-1} 1590, 1620; NMR ($CDCl_3$) δ 2.85 - 3.15 (m, 2, $H_{6',6''}$), 3.30 - 3.70 (m, 4, CH_2CH_2), 4.80 - 9.00 (m, 1, H_5), 9.20 - 5.30) (m, 1, H_2), 5.47 (d, $\underline{J}_{1-2}$ = 3 Hz, 1, H_1), 5.70 - 6.00 (m, 2, $H_{3,4}$), 6.50 - 7.50 (m, 25, C_6H_5); MS m/e 564.2777 (2.68, M^+, calcd for $C_{39}H_{36}N_2O_2$: 564.2777).

Anal. Calcd for $C_{39}H_{36}N_2O_2$: C, 82.98; H, 6.38; N, 4.96. Found: C, 83.17; H, 6.58; N, 4.83.

3,6-Anhydro-4,5,7-tri-O-benzyl-D-glycero-D-(allo and altro)-heptonamide (68)

A solution of p-toluenesulfonic acid monohydrate (5.9 g, 30.3 mmol) in acetone (5 ml) was added to a stirred solution of the imidazolidine sugar [56] (67) (6.5 g, 10.3 mmol) in methylene chloride (100 ml) at 0°C. After stirring for 15 min at 0°C followed by 30 min at room temperature, an additional 500 mg of p-toluenesulfonic acid monohydrate in acetone (1 ml) was added. After a total reaction time of 1 h, the mixture was diluted with methylene chloride (100 ml) filtered through celite, washed with saturated brine (3 x 20 ml), dried and evaporated. The residue was dissolved in 1,4-dioxane, cooled to 10°C, and treated with sodium cyanide (8.7 g) and potassium carbonate (8.7 g) in water (100 ml). After stirring at 0°C for 30 min the reaction was treated dropwise with 30% hydrogen peroxide (30 ml). After stirring for 1 h at 0°C the mixture was poured into water (3 L). The precipitate was filtered and dried to give 4.5 g (91%) of 68. TLC revealed the presence of a trace of impurity: ($CHCl_3$/EtOAc 1:1, impurity R_f = 0.8, product R_f = 0.2).

3,6-Anhydro-4,5,7-tri-O-benzyl-2-O-methanesulfonyl-D-glycero-D-(allo and altro)-heptonamide (69 and (70)

A solution of the α-hydroxy amide[57] (68) (4.77 g, 10 mmol) in pyridine (25 ml) and methylene chloride (35 ml) at 0°C was treated dropwise with methanesulfonyl chloride (5.7 g, 4.05 ml, 50 mmol) in methylene chloride (15 ml). After 7 h at 0°C the reaction was diluted with methylene chloride (200 ml) and poured into ice cold 1N hydrochloric acid (100 ml). The organic layer was washed with 1N hydrochloric acid (2 x 50 ml), saturated sodium bicarbonate (3 x 25 ml), saturated brine (3 x 25 ml), dried and evaporated to a solid. This was triturated with hot ether (100 ml) and filtered to give 2.4 g (43%) of 69. TLC (ethyl acetate-chloroform (1:1) R_f = 0.4) revealed this to be the faster migrating isomer. This product was recrystallized from methanol to give 2.1 g (85%) of pure white needles: mp 173 - 174°C; $[\alpha]_D^{23}$ + 65° (c 0.2, $CHCl_3$); IR (KBr) 1650 cm^{-1} ($CONH_2$); NMR ($CDCl_3$) δ 2.91 (s, 3, SO_3CH_3), 3.44 and 3.71 ("octet", $J_{7-7'}$ = 10 Hz, J_{7-6} = 3 Hz, $J_{7'-6}$ = 2.5 Hz, 2, $H_{7,7'}$), 3.85 - 4.80 (m, 10, sugar and $CH_2C_6H_5$), 4.90 (d, J_{2-3} = 5 Hz, 1, H_2), 5.7 and 6.5 (bs, 2, $CONH_2$), 7.30 (m, 15, C_5H_5); MS m/e 555.1954 (1.0, M$^+$, calcd for $C_{29}H_{33}NO_8S$: 555.1927), 476.2074 (0.57, M$^+$ - SO_2CH_3), 465.1409

(25.97, $M^+ + 1-CH_2C_6H_5$), 464.1374 (100, $M^+ - CH_2C_6H_5$), 449.1501 (2.41, $M^+ + 1 - OCH_2C_6H_5$), 448.1416 (2.7, $M^+ - OCH_2C_6H_5$), 358.0963 ($M^+ - CH_2C_6H_5 - OCH_2C_6H_5$).

Anal. Calcd for $C_{29}H_{33}NO_8S$: C, 62.70; H, 5.95; N, 2.52; S, 5.76. Found: C, 62.83; H, 6.07; N, 2.54; S, 5.78.

The residual syrup was chromatographed on silica (40 g, 3 x 14 cm). Elution with solvent G gave 2.1 g (38%) of *70* as a white solid. This slower migraging isomer was crystallized from ether (50 ml) to give a solid (1.2 g) which contained a trace of the "TOP" isomer as seen by TLC: mp 114 - 11[illegible]°C; $[\alpha]_D^{23}$ + 30° (*c*, 0.2, $CHCl_3$), NMR ($CDCl_3$) δ 2.86 (s, 3, SO_3CH_3), 3.47, 3.62 (m, J_{7-7} = 11 Hz, J_{7-6} = 4 Hz, $J_{7'-6}$ = 3.5 Hz, 2, $H_{7,7'}$), 3.80 - 4.70 (m, 10, sugar and $\underline{CH_2}C_6H_5$), 4.91 (d, J_{2-3} = 4 Hz, 1, H_2), 5.9 and 6.4 (bs, 2, $CONH_2$), 7.25 (m, 15, C_6H_5); MS m/e 555.1928 (0.33, M^+, calcd for $C_{29}H_{33}NO_8S$: 555.1927), 476.2049 (0.06, $M^+ - SO_2CH_3$); 465.1426 (11.0; $M^+ + 1 - CH_2C_6H_5$), 464.1392 (41.78, $M^+ - CH_2C_5H_5$), 449.1481 (0.75, $M^+ + 1 - OCH_2C_6H_5$).

3,6-Anhydro-2-azido-2-deoxy-4,5,7-tri-*O*-benzyl-D-glycero-D-(altro and allo)-heptonamide (*71* and *72*).

A solution of the α-mesyl amide (*69* or *70*) (1.11 g, 2 mmol) and lithium azide (245 mg, 5 mmol) in dimethylformamide (40 ml) was heated at 100°C for 6[illegible], cooled and poured into ether (100 ml) and 5% aqueous sodium chloride (25 ml). The aqueous layer was extracted with ether (3 x 25 ml). The combined organic fractions were evaporated to a syrup and purified by chromatography on silica (20 g, 12 x 2.2 cm). Elution with solvent G gave the desired product.

"Faster" isomer (71): The yield after chromatography was 980 mg (98%). This solid was crystallized from ethanol in approximately 50 - 70% recovery: mp 93 - 94°C; $[\alpha]_D^{23}$ + 13° (*c* 0.2, $CHCl_3$); IR (KBr) 1670 cm^{-1} ($CONH_2$), 2110 cm^{-1} (N_3); NMR ($CDCl_3$) δ 3.46, 3.57 (m, $J_{7-7'}$ = 10 Hz), J_{7-6} = 4 Hz, $J_{7'-6}$ = 3.5 Hz, 2, $H_{7,7'}$), 3.80 - 4.20 (m, 11, sugar and $CH_2C_6H_5$), 5.8 and 6.3 (bs, 2, $CONH_2$), 7.3 (s, 15, C_6H_5); MS m/e 474.2157 (4.81, M^+-N_2, calcd for $C_{28}H_{30}N_2O_5$: 474.2155) 384.1646 (1.17, $M^+ + 1 - N_2 - CH_2C_6H_5$), 383.1610 (4.59, $M^+ - N_2 - CH_2C_6H_5$), 368.1734 (2.18, $M^+ + 1 - N_2 - OCH_2C_6H_5$).

Anal. Calcd for $C_{28}H_{30}N_4O_5$: C, 66.93; H, 5.97; N, 11.15. Found: C, 66.57; H, 6.06; N, 11.11.

"Slower" isomer (72): The yield after chromatography was 920 mg (92%). This solid was crystallized in approximately 70% recovery from ether - Skelly "B": mp 155 - 156°C; $[\alpha]_D^{23}$ + 10° (*c* 0.2, $CHCl_3$); NMR ($CDCl_3$) δ 3.92 and 3.60 (octet, $J_{7-7'}$ = 10 Hz, J_{7-6} = 3.5 Hz, $J_{7'-6}$ = 4 Hz, 2, $H_{7,7'}$), 3.80 - 4.70 (m, 11, sugar and

$\underline{CH_2}C_6H_5$, 6.0 and 6.4 (bs, 2, $CONH_2$), 7.3 (s, 15, C_6H_5); MS m/e 503.2268 (2.13, $M^+ + 1$), 502.2179 (0.21, M^+, calcd for $C_{28}H_3ON_4O_5$: 502.2189), 475.2211 (6.66, $M^+ + 1 - N_2$), 474.2147 (11.08, $M^+ - N_2$), 384.1645 (1.79, $M^+ - N_2 - CH_2C_6H_5$).

Anal. Calcd for $C_{28}H_{30}N_4O_5$: C, 66.93; H, 5.97; N, 11.15. Found: C, 66.96; H, 6.11, N, 10.97.

2(S)-Amino-2(β-D-ribofuranosyl)ethanoic acid (*75*) or L-glycine ribose and 2(R)amino-2(β-D-ribofuranosyl)ethanoic acid (*76*) or D-glycine ribose.

A solution of the tri-*O*-benzyl protected α-azido amide (*71* or *72*) (502 mg, 1 mmol) in 1,4-dioxane (10 ml) and 50% HCl/H_2O (2 ml) was stirred at 80°C for 18 h, cooled, diluted with water (20 ml) and extracted with chloroform (3 x 20 ml). The combined organic layers were washed with saturated brine (3 x 10 ml), dried and evaporated to give 510 mg (quantitative) of a colorless stiff syrup. This was dissolved in ethanol (40 ml) and 1*M* NH_4OAc-HOAc (10 ml, adjusted to pH 5 with HOAc) and hydrogenated over 5% Pd-C (500 mg) at 100 psi for 48 h. After this time the reaction was filtwered through celite and the catalyst was washed with 95% ethanol (25 ml) and H_2O (25 ml). The combined filtrates were evaporated to a syrup and applied to a column of ANGC(H^+) resin (20 gm). The column was washed well with water (until the eluants were neutral) followed by 0.5N NH_4OH. The ninhydrin positive fractions were collected and evaporated under vacuum to give 110 mg (53% yield) of 75 or 76 as a tan colored solid, which migrated as one spot on paper chromatography [solvent system M (R_f = 0.25) solvent system N (R_f = 0.07)]. Crystallization of 75 from ethanol-water gave fine colorless needles: mp 208 210°C (d); $[\alpha]_D^{23}$ - 12° (c 0.1, H_2O); IR (FT) (KBr) 1640 cm^{-1} (CO_2H), 3400 cm^{-1} (OH); ORD (6N HCl) $[\phi]_{225}$ = +2,000; CD (6N HCl) $[\theta]_{210}$ = +2,010.

Anal. Calcd for $C_7H_{13}NO_6 \cdot 3/4H_2O$: C, 38.36; H, 6.62; N, 6.39. Found: C, 38.05; H, 6.57; N, 6.10.

The remaining isomer 76 was isolated as an amorphous solid: mp 120°C (d); $[\alpha]_D$ - 4° (c 0.1, H_2O); ORD (6N HCl) $[\phi]_{225}$ = -2,300; CD (6N HCl) $[\theta]_{210}$ = -1850.

1,3-Diphenyl-2-(5-O-trityl-2,3-di-O-benzyl-β-D-ribofuranosyl)imidazolidine (77)

The imidazolidine sugar (64) (3.0 g, 5 mmol) in DMF (12.5 ml) was added to a suspension of NaH (960 mg, 50% oil suspension, 20 mm) in DMF (5 ml) under nitrogen at 0°C. After 2 h at room temperature the solution was cooled to 0°C and treated dropwise with benzyl bromide (2.38 ml, 3.42 g, 20 mmol) in DMF (7.5 ml) over a period of 30 min. The mixture was then stirred at room temperature for 2.5 h, carefully quenched with MeOH (1 ml) and poured into a mixture of ether (200 ml) and H_2O (200 ml). The aqueous layer was extracted with ether (3 x 25 ml). The combined organic layers were washed with saturated brine (3 x 10 ml), dried and evaporated to a brown syrup which was purified by chromatography on silica (100 g, 4.5 x 18 cm). Elution with Skelly "B" followed by solvent F and then solvent D gave 3.45 g (88%) of 77 as a pale solid foam homogeneous by TLC (Skelly "B"/ether 1:1 R_f = 0.7): $[\alpha]_D^{23}$ + 8° (c 0.1, $CHCl_3$); UV (MeOH) max 255 nm (ε 32,000), shoulder 293 nm (ε 4,200); NMR ($CDCl_3$) δ 3.00 - 4.60 (m, 14, sugar and CH_2CH_2), 5.67 (bs, 1, H_1), 6.60 - 7.50 (m, 35, C_6H_5); MS m/e 778 (M^+), 670 ($M^+ - HOCH_2C_6H_5$), 562 ($M^+ - 2(HOCH_2C_6H_5)$).

1,3-Diphenyl-2-(5-O-dimethoxytrityl-2,3-di-O-benzyl-β-D-ribofuranosyl)imidazolidine (77a)

A solution of the imidazolidine sugar (63) (5.0 g, 0.75 mmol) in dimethylformamide (20 ml) was added at 0°C to a suspension of sodium hydride (1.48 g, 50% oil suspension, 3 mmol) in dimethylformamide (8 ml) under nitrogen. After 2 h at room temperature the reaction was cooled to 0°C and treated dropwise with benzylbromide (5.26 g, 3.65 ml, 3 mmol) in dimethylformamide (12 ml). After 2 h at room temperature, the reaction was quenched with methanol (2 ml) and poured into a mixture of ether (100 ml) and 5% aqueous sodium chloride solution (50 ml). The aqueous layer was extracted with ether (3 x 25 ml). The combined organic layers were washed with saturated brine (3 x 25 ml) dried and evaporated to a syrup which was purified by chromatography on silica (100 g, 4.5 x 18 cm). Elution with Skelly "B" followed by solvent D gave 5.4 g (85%) of 77a as a pale yellow foam: $[\alpha]_D^{23} + 4$ (c 0.1, $CHCl_3$); UV (MeOH) max 239 nm (ε 33,000), max 253 (ε 33,500), shoulder 238 (ε 5,700); NMR ($CDCl_3$) δ 2.90 - 4.80 (m, 15, sugar and C_2H_2), 3.75 (s, 6, OCH_3), 5.58 (bs, 1, H), 6.60 - 7.50 (m, 33, C_6H_5 and C_6H_4); MS m/e 838 (M^+, $C_{56}H_{54}N_2O_6$), 730 (M^+-$HOCH_2C_6H_5$), 622 (M^+-2($HOCH_2C_6H_5$)), 303 ($C_{21}H_{19}O_2$), 223 ($C_{15}H_{15}N_2$).

3,6-Anhydro-4,5-di-O-benzyl-D-glycero-D-(allo and altro)-heptonamide (79)

A solution of the trityl-protected imidazolidine sugar (77) (7.78 g, 10 mmol) in methylene chloride (150 ml) was treated with p-toluenesulfonic acid monohydrate (7.6 g, 40 mmol) in acetone (10 ml) and stirred at room temperature for 50 min. The solution was diluted with methylene chloride, filtered through celite, neutralized with pyridine (1 ml), and evaporated to a syrup. The residue was purified by chromatography on silica (80 g, 23 x 3 cm). Elution with chloroform followed by solvent A and then ethyl acetate gave 2.8 g (82%) of 78: MS m/e 342.1466 (0.07, M^+, calcd for $C_{20}H_{22}O_5$: 342.1466), 251.0915 (28.88, $M^+-CH_2C_6H_5$), 234.0887 (3.30, $M^+-HOCH_2C_6H_5$).

This syrup was dissolved in 1,4-dioxane (80 ml), cooled to 5°C and treated with sodium cyanide (4 g) and potassium carbonate (4 g) in water (60 ml). After 30 min at room temperature the mixture was cooled to 0°C and treated with 30% hydrogen peroxide (19 ml). After 1 h at 0°C the mixture was diluted with water (100 ml) and ethyl acetate (100 ml). The aqueous solution was saturated with sodium chloride and extracted with ethyl acetate (4 x 25 ml). The combined organic fractions were washed with saturated brine (3 x 10 ml), dried and evaporated to give 2.95 g (93%) of 79, homogeneous by TLC (ethyl acetate-chloroform (1:1) $R_f \approx 0.1$; ethyl acetate, $R_f \approx 0.3$). One isomer fractionally crystallized from chloroform in approximately 10% yield and proved difficult to recrystallize: mp 181 - 182°C; $[\alpha]_D^{23} + 76°$ ($\underline{c}$ 0.1, acetone); IR (KBr) 3400 cm^{-1} (OH, $CO\underline{NH}_2$), 1680 cm^{-1} ($CONH_2$); NMR (acetone-d_6) δ 3.50 - 3.90 (m, $\underline{J}_{7-6}$ = 3 Hz, $\underline{J}_{7'-6}$ = 3 Hz, $\underline{J}_{7-7'}$ = 12 Hz, 2, $H_{7-7'}$), 4.00 - 4.90 (m, 11, $H_{2,3,4,5,6}$, OH, $\underline{CH}_2C_6H_5$), 6.65 - 7.10 (bd, 2, $CONH_2$), 7.3 (m, 10, C_6H_5); MS m/e 388.1764 (1.46, $M^+ + 1$, calcd for

$C_{21}H_{26}NO_6$: 388.1760), 297.1172 (3.45, $M^+ + 1 - CH_2C_6H_5$), 296.1131 (23.03, $M^+ - CH_2C_6H_5$), 281.1255 (0.72, $M^+ + 1 - OCH_2C_6H_5$), 280.1190 (1.03, $M^+ - OCH_2C_6H_5$).

Anal. Calcd for $C_{21}H_{25}NO_6$: C, 65.12; H, 6.46; N, 3.62. Found: C, 65.10; H, 6.39; N, 3.70.

3,6-Anhydro-4,5-di-O-benzyl-N,O_2-isopropylidene-7-O-methanesulfonyl-D-glycero-D-(allo and altro)-heptonamide (82)

A solution of the α-hydroxy amide (79) (4.26 g, 11 mmol) in acetone was treated with perchloric acid (0.6 ml of 70% solution) and allowed to stand at room temperature. After 4.5 h the dark brown solution was neutralized with concentrated ammonium hydroxide (solution turned pale yellow) and then concentrated to a syrup. This residue was dissolved in chloroform (100 ml) washed with saturated brine (3 x 10 ml), dried and evaporated. The residue was co-evaporated with benzene (20 ml) to give (81) as a syrup: MS m/e 428 (0.3, $M^+ + 1$), 427 (0.8, M^+), 412 (0.5, $M^+ - CH_3$), 336 (11.7, $M^+ - CH_2C_6H_5$). This syrup was dissolved in methylene chloride (50 ml) and pyridine (25 ml), cooled to 0°C and treated dropwise with methanesulfonyl chloride (6.27 g, 55 mmol) in methylene chloride (25 ml). After 12 h at 0°C the mixture was treated with ice water (25 ml) and extracted with methylene chloride (3 x 10 ml). The combined organic phase was washed with saturated brine (3 x 20 ml), dried, evaporated to a syrup and purified by chromatography on silica (100 g, 12 x 4.5 cm). Elution with solvent B, followed by ethyl acetate gave 5.1 g (92%) of 82 as a stiff syrup: IR (film) 3250 cm^{-1} (CONHR), 1720 (CONHR), 1360, 1180 (SO_3CH_3); NMR ($CDCl_3$) δ 1.29 and 1.38 (s+s, c, $C(CH_3)_2$, isomer "A"), 1.39 and 1.42 (s+s, 3, $C(CH_3)_2$, isomer "B"), 2.91 (s, 3, SO_3CH_3, isomer "B"), 2.93 (s, 3, SO_3CH_3, isomer "A"), 3.70 - 4.60 (m, 11, sugar), 7.3 (s, 10, C_6H_5), 8.05 (bs, 1, CONHR, isomer "A), 8.42 (bs, 1, CONHR, isomer "B"); MS m/e 506.1857 (0.07, M^++1), 505.1774 (0.15, M^+, calcd for $C_{25}H_{31}NO_8S$: 505.771); 491.1599 (0.18, M^++1-CH_3), 490.1530 (7.79, M^+-CH_3), 415.1267 (1.89, M^++1-$CH_2C_6H_5$), 414.1233 (9.32, M^+-$CH_2C_6H_5$), 400.1415 (0.06, M^++1-CH_3-$CH_2C_6H_5$), 399.1372 (0.29, M^+-CH_3-$CH_2C_6H_5$), 309.0837 (0.75, M^++1-CH_3-2$CH_2C_6H_5$), 308.0800 (5.99, M^+-CH_3-2$CH_2C_6H_5$).

Anal. Calcd for $C_{25}H_{31}NO_8S$: C, 59.40; H, 6.14; N, 2.77; S, 6.34. Found: C, 58.70; H, 6.27; N, 2.66; S, 6.53.

3,6-Anhydro-4,5-di-O-benzyl-7-deoxy-N,O$_2$-isopropylidene-D-glycero-D-(allo and altro)-heptonamide (84)

A solution of the 7-O-mesyl derivative (82) (4.55 g, 0.9 mmol) in methyl ethyl ketone (250 ml) was treated with sodium iodide (2.7 g, 18 mmol), refluxed for 20 h, cooled and evaporated to a yellow paste. This residue was dissolved in chloroform (150 ml) washed with 5% aqueous sodium bisulfite solution (2 x 20 ml), saturated brine (2 x 20 ml), dried and evaporated to give 5.0 g of 83 as a viscous syrup: MS m/e 538.1062 (0.18, $M^{+}+1$), 537.1020 (0.19, M^{+}, calcd for $C_{24}H_{28}NO_5I$: 537.1012), 523.0828 (0.23, $M^{+}+1-CH_3$), 522.0791 (0.60, $M^{+}-CH_3$), 446.0468 (22.54, $M^{+}-CH_2C_6H_5$), 431.0588 (0.35, $M^{+}+1-OCH_2C_6H_5$).

This syrup was dissolved in 98% ethanol (100 ml) treated with triethylamine (10 ml) and a chip of dry ice, and hydrogenated at 15 psi over 5% Pd/c (500 mg). After 6 h the mixture was filtered and evaporated to a syrup. The residue was dissolved in chloroform (100 ml), washed with 5% aqueous sodium bisulfite (2 x 10 ml), saturated brine (2 x 10 ml), dried and evaporated. The product was chromatographed on silica (60 g, 3 x 18 cm), eluting with solvent G followed by ethyl acetate to give 3.04 g (82%) of 84 as a syrup: IR (film) 1720 cm^{-1} ($\underline{CO}NH_2$), 3250 cm^{-1} ($CO\underline{NH_2}$); NMR ($CDCl_3$) δ 1.21 and 1.25 (d+d, $\underline{J}_{7-6} \approx 6$ Hz, 3, H_7), 1.29 and 1.40, 1.40 and 1.43 (4 singlets, 6, $C(CH_3)_2$, isomer a, isomer b), 3.4-5.7 (m, 9, sugar and $\underline{CH_2}C_6H_5$), 7.35 (s, 10, C_6H_5), 8.35 and 8.61 (bs, 1, CONHR); MS m/e 411.2049 (0.86, M^{+}, calcd for $C_{24}H_{29}NO_5$: 411.2046), 396.1806 (0.97, $M^{+}-CH_3$), 320.1483 (41.26, $M^{+}-CH_2C_6H_5$), 305.1612 (0.6, $M^{+}-CH_3-CH_2C_6H_5$), 214.1069 (30.54, $M^{+}-CH_3-2.CH_2C_6H_5$).

Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.07; H, 7.05; N, 3.41. Found: C, 69.24, H, 7.30; N, 3.31.

Methyl 3,6-anhydro-7-deoxy-4,5-di-O-benzyl-D-glycero-D-(allo and altro)-heptonoate (85)

A solution of the isopropylidene derivative (84) (1.03 g, 2.5 mmol) in MeOH (30 ml) was treated with ANGC (H^+) resin (2.5 g) and stirred under reflux. After 10 h an additional 2.5 g of resin was added. After 30 h TLC revealed the reaction was complete (EtOAc/Skelly "B" 1:1, product $R_f \approx 0.7$, starting material $R_f \approx 0.5$). The mixture was filtered through a celite pad, evaporated to a syrup, and purified by chromatography on silica (50 gm, 3 x 20 cm). Elution with solvent H followed by solvent B gave 680 mg (70%) of 85 as a syrup: IR (film) 1745 cm^{-1} (CO_2Me), 3540 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.16 (d, J_{6-7} = 6.5 Hz, 3, H_7, isomer A), 1.19 (d, J_{6-7} = 6.5 Hz, 3, H_7, isomer B), 2.95 (bs, 1, OH), 3.62 (s, 3, OCH_3, isomer A), 3.72 (s, 3, OCH_3, isomer B), 3.40 - 4.65 (m, 9, sugar and $CH_2C_6H_5$), 7.30 (s, 10, C_6H_5); MS m/e 386.1717 (0.06, M^+, calcd for $C_{22}H_{26}O_6$: 386.1730), 295.1170 (23.24, $M^+-CH_2C_6H_5$).

Methyl 3,6-anhydro-7-deoxy-4,5-di-O-benzyl-2-O-methane sulfonyl-D-glycero-D-(allo and altro)-heptonoate (86)

A solution of the α-hydroxy ester (85) (580 mg, 1.5 mmol) in methylene chloride (5 ml) and pyridine (5 ml) at 0°C was treated dropwise with methanesulfonyl chloride (350 mg, 3 mmol) in methylene chloride (2 ml). The solution was allowed to stand at 0°C for 1 h, at room temperature for 3 h, and then was treated with ice water and extracted with chloroform (3 x 25 ml). The organic phase was washed with 1N hydrochloric acid (2 x 10 ml), saturated aqueous sodium bicarbonate (2 x 10 ml), saturated brine (2 x 10 ml), dried and evaporated to a syrup. This residue was purified by chromatography on silica (10 g, 1.8 x 13 cm), eluting with solvent H to give 615 mg (88%) of 86 as a syrup: IR (film) 1760 cm^{-1} (CO_2CH_3), 1365 and 1180 (SO_3CH_3); NMR ($CDCl_3$) δ 1.17 (d, J_{7-6} = 6.5 Hz, 3, H_7, isomer A), 1.19 (d, J_{7-6} = 6.5 Hz, 3, H_7, isomer B), 3.04 (s, 3, SO_3CH_3, isomer B), 3.14 (s, 3, SO_3CH_3, isomer A), 3.68 (s, 3, CO_2CH_3, isomer B), 3.76 (s, 3, CO_2CH_3, isomer A), 3.40 - 4.60 (m, 8, sugar and C_6H_5), 5.05 (d, J_{2-3} = 2.5 Hz, 1, H_2, isomer A), 5.12 (d, J_{2-3} = 3 Hz, 1, H_2, isomer B); MS m/e 373.0950 (26.05, $M^+ - CH_2C_6H_5$, calcd for $C_{16}H_{21}O_8S$: 373.0957).

Methyl 3,6-anhydro-7-deoxy-2-O-methanesulfonyl-4,5-thiocarbonato-D-glycero-D-(allo and altro)-heptonoate (88)

A solution of the 4,5-di-O-benzyl α-mesyl ester (86) (600 mg, 1.3 mmol) in 98% ethanol was hydrogenated over 5% Pd-C (600 mg) at 100 psi in a Parr pressure vessel. After 48 h the mixture was filtered through celite and evaporated to give 260 mg (quantitative) of 87 as a syrup.

This residue was dissolved in acetone (10 ml) and treated with dimidazole thiocarbonate (1.1 g, 6 mmol). After 40 h the solution was evaporated. The residue was dissolved in ethyl acetate (30 ml), washed with 0.5N hydrochloric acid (2 x 10 ml), saturated brine (2 x 10 ml), dried and evaporated. This residue was rapidly chromatographed on silica (10 g, 1.8 x 13 cm), eluting with solvent B to give 400 mg (95%) of 88 as a syrup: IR (film) 1760 cm^{-1} (CO_2CH_3); UV (MeOH) max 237 nm; NMR ($CDCl_3$) δ 1.39 (d, J_{7-6} = 6 Hz, 3, H_7, isomer A), 1.43 (d, J_{7-6} = 6 Hz, 3, H_2, isomer B), 3.12 (s, 3, SO_3CH_3, isomer B), 3.22 (s, 3, SO_3CH_3, isomer A), 3.82 (s, 3, CO_2CH_3, isomer B), 3.84 (s, 3, CO_2CH_3, isomer A), 4.00 - 4.3 (m, 1, H_6), 4.50 - 5.00 (m, 2, H_3 and H_5), 5.20 - 5.45 (m, 2, H_2 and H_4); MS m/e 326.0125 (67.06, M^+, calcd for $C_{10}H_{14}O_8S_2$: 326.0130).

Methyl 3,6-anhydro-4,5,7-tri-deoxy-2-O-methanesulfonyl-D-(ribo and arabino)-hept-4-enoate (89)

A solution of the thiocarbonate sugar derivative

(88) (350 mg, 1.07 mmol) in trimethylphosphite (5 ml) was refluxed under nitrogen for 4 h, concentrated under reduced pressure to remove excess trimethylphosphite, and rapidly chromatographed on silica (10 g, 1.8 x 13 cm). Elution with solvent K gave 220 mg (82%) of 89 as a clear viscous syrup. One isomer was fractionally crystallized from ether-Skelly "B" (~30%): mp 106 - 107°C; $[\alpha]_D^{23}$ - 14° (c 0.1, $CHCl_3$); IR (KBr) 1730 cm^{-1} (CO_2CH_3), 1620 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.28 (d, J_{7-6} = 6 Hz, 3, H_7), 3.13 (s, 3, SO_3CH_3), 3.82 (s, 3, CO_2CH_3), 4.95 (m, 1, H_6), 5.01 (d, J_{2-3} = 3 Hz), 5.30 (m, 1, H_3), 5.7 (m, 1, H_5), 6.00 (m, 1, H_4); MS CI(NH_3) 268 (M^+ + 18), 518 (2m + 18).

Anal. Calcd for $C_9H_{14}SO_6$: C, 43.20; H, 5.60; S, 12.80. Found: C, 43.27; H, 5.72; S, 12.44.

1,3-Diphenyl-2-(5-O-benzyl-2,3,O-isopropylidene-β-D-ribofuranosyl)imidazolidine (90)

A solution of the isopropylidene-protected imidazolidine sugar (45) (3.96 g, 10 mmol) in dimethylformamide (20 ml) was added to a stirred suspension of NaH (960 mg, 50% oil suspension, 20 mmol) in dimethylformamide (5 ml) at 0°C under N_2. After 1 h at room temperature the solution was cooled to 0°C and treated dropwise with benzylbromide (2.38 ml, 3.4 g, 10 mmol) in dimethylformamide (10 ml). The mixture was stirred at room temperature for 3 h, quenched with methanol (2 ml), and poured into a mixture of methylene chloride (50 ml) and water (50 ml). The aqueous layer was extracted with methylene chloride (3 x 25 ml). The combined organic phase was washed with saturated brine (10 ml), dried and evaporated to a white solid. This solid was crystallized from methanol-chloroform to give 4.45 g (91%) of 90: mp 148 - 149°C; $[\alpha]_D^{23}$ - 14° (c 0.11, $CHCl_3$); UV (MeOH) max 253 nm (ε 31,800), shoulder 293 nm (ε 4,100); NMR ($CDCl_3$) δ 1.24 and 1.38 (s+s, 3+3, $C(CH_3)_2$), 3.40 - 4.80 (m, 6, CH_2CH_2), 4.05 (q, $\underline{J}_{5-6,6'}$ = 5 Hz, 1, H_5), 4.25 - 4.40 (m, 2, H_2 and H_4), 4.50 (s, 2, $\underline{CH_2}C_6H_5$), 4.63 (d of d, J = 5 Hz, J = 6.5 Hz, 1, H_3), 5.58 (d, $\underline{J}_{1-2}$ = 2 Hz, 1, H_1), 6.60 - 7.40 (m, 15, C_6H_5); MS m/e 486.2525 (0.47, M^+, calcd for $C_{30}H_{34}N_2O_4$: 486.2518), 471 (M^+-CH_3), 380 (M^+-CH_3 - NC_6H_5), 223 ($C_{15}H_{15}N_2$).

Anal. Calcd for $C_{30}H_{34}N_2O_4$: C, 74.07; H, 6.99; N, 5.76. Found: C, 74.21; H, 7.21; N, 5.80.

3,6-Anhydro-7-O-benzyl-4,5-O-isopropylidene-D-glycero-D-(allo and altro)heptonamide (91 and 92)

A stirred solution of the 7-O-benzyl imidazolidine sugar (90) (12.15 g, 25 mmol) in methylene chloride (250 ml) at 0°C was treated with p-toluenesulfonic acid monohydrate (14.25 g, 75 mmol) in acetone

(20 ml). After 15 min an additional 1 g of the acid in acetone (5 ml) was added. After a total reaction time of 20 min the mixture was diluted with methylene chloride (200 ml) and filtered through a celite pad. The filtrate was treated with solid $NaHCO_3$ (25 g), refiltered through celite and evaporated to a syrup. This residue was dissolved in 1,4-dioxane (250 ml) cooled to 5°C and treated with sodium cyanide (18 g) and potassium carbonate (18 g) in water (250 ml). After 30 min at room temperature the solution was cooled to 0°C and treated dropwise with 30% hydrogen peroxide (125 ml) over a period of 30 min. The mixture was stirred at 0°C for an additional 30 min, (the reaction temperature slowly rose to 35°C then subsided) and was then diluted with water (600 ml) (to dissolve the solid precipitate) and ethyl acetate (250 ml). The aqueous phase was saturated with sodium chloride and extracted with ethyl acetate (3 x 50 ml). The combined organic phase was washed with saturated brine (3 x 20 ml), dried, concentrated to approximately 10 ml and diluted with ether (100 ml). The solid that crystallized was filtered to give 3.65 g (43%) of 91 (faster migrating isomer by TLC).

"Faster" isomer: mp 133 - 135°C; $[\alpha]_D^{23}$ + 39° (c 0.1, $CHCl_3$); IR (KBr) 1650 cm^{-1} ($CONH_2$), 3300 - 3500 cm^{-1} (OH, $CO\underline{NH_2}$); NMR ($CDCl_3$) δ 1.31 and 1.50 (s+s, 3+3, $C(CH_3)_2$), 3.53 and 3.73 (ABX, "octet", $\underline{J}_{6-7}$ = 3.2 Hz,

$\underline{J}_{6-7'}$ = 2.7, $\underline{J}_{7-7'}$ = 12 Hz, 2, H_7 and $H_{7'}$), 4.10 - 4.75 (m, 11, sugar and $\underline{CH}_2C_6H_5$), 5.7 and 6.7 (bs, 2, $CONH_2$), 7.3 (s, 5, C_6H_5); MS m/e 338.1599 (0.78, M^++1, calcd for $C_{17}H_{24}NO_6$: 338.1604), 337.1539 (2.34, M^+), 323.1341 (1.63, M^++1-CH_3), 322.1308 (7.52, M^+-CH_3), 263.1290 (12.24, M^+-$C_2H_4NO_2$).

Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.53; H, 6.82; N, 4.15. Found: C, 60.35; H, 6.93; N, 3.93.

The mother liquors were concentrated and purified by chromatography on silica (50 g, 3 x 15 cm). Elution with solvent B followed by ethyl acetate gave 3.67 g (43%) of 92 as a syrup with only a minor amount (<5%) of 91.

"Slower" isomer: $[\alpha]_D^{23}$ - 10°; NMR ($CDCl_3$) δ 1.32 and 1.52 (s+s, 3+3), 3.56 and 3.76 (ABX, "octet", $\underline{J}_{6-7}$ = 3 Hz, $\underline{J}_{6-7'}$ = 3 Hz, $\underline{J}_{7-7'}$ = 12 Hz, 2, H_7 and $H_{7'}$), 4.10 - 4.75 (m, 11, sugar and $\underline{CH}_2C_6H_5$), 6.3 and 6.7 (bs, 2, $CONH_2$), 7.3 (s, 5, C_6H_5).

3,6-Anhydro-2-O-acetyl-7-O-benzyl-4,5-O-isopropylidene-D-glycero-D-(allo and altro)-heptonamide (93 and 94)

A solution of the α-hydroxy amide (91, 92) (11.8 g, 3.5 mmol) in pyridine (200 ml) at 0°C was treated with acetic anhydride (10 ml, 9.26 g, 9 mmol). After 1 h at 0°C the solution was allowed to stand at room temperature for 12 h, treated with ice and diluted with methylene chloride (250 ml). The organic phase was washed with 1N hydrochloric acid, 5% sodium bicarbonate solution, saturated brine (3 x 25 ml), dried and evaporated to give 93 or 94 (13.6 g, quantitative).

The "faster" migrating isomer (93) was obtained as a viscous syrup: $[\alpha]_D^{23} - 14°$ (c 0.1, $CHCl_3$); IR (film) 1700 cm^{-1} ($\underline{CO}NH_2$), 1750 cm^{-1} ($\underline{CO}CH_3$), 3300 cm^{-1} ($CO\underline{NH_2}$); NMR ($CDCl_3$) δ 1.33 and 1.52 (s+s, 3+3, $C(CH_3)_2$), 2.06 (s, 3, $COCH_3$), 3.48 and 3.69 (ABX, "multiplet", $\underline{J}_{6-7}$ = 5 Hz, $\underline{J}_{6-7'}$ = 3.7 Hz, $\underline{J}_{7-7'}$ = 11 Hz, 2, H_7 and $H_{7'}$), 4.05 - 4.30 (m, 1, H_6), 4.28 and 4.33 (d of d, $\underline{J}_{3-2}$ = 5.5 Hz, $\underline{J}_{3-4}$ = 3.2 Hz, 1, H_3), 4.52 (s, 2, $\underline{CH_2}C_6H_5$), 4.50 - 4.65 (d of d, $\underline{J}_{5-4}$ = 3.5 Hz, 1, H_5), 4.78 and 4.81 (d of d, $\underline{J}_{4-3}$ = 3.2 Hz, $\underline{J}_{4-5}$ = 3.5 Hz, 1, H_4), 5.23 (d, $\underline{J}_{2-3}$ = 5.5 Hz, 1, H_2), 6.00 - 6.50 (bd, 2, $CONH_2$), 7.30 (s, 5, C_6H_5); MS m/e 379.1639 (0.33, M^+, calcd for $C_{19}H_{25}NO_7$: 379.1631), 364.1393 (5.10, M^+-CH_3).

Anal. Calcd for $C_{19}H_{25}NO_7$: C, 60.16; H, 6.59; N, 3.69. Found: C, 59.91; H, 6.57; N, 3.62.

The "slower" migrating isomer (94) was obtained as a viscous syrup $[\alpha]_D^{23} + 21°$ (c 0.1, $CHCl_3$); NMR ($CDCl_3$) δ 1.33 and 1.52 (s+s, 3+3, $C(CH_3)_2$), 2.08 (s, 3, $COCH_3$), 3.00 (apparent d, $\underline{J}_{6-7}$ = 4 Hz, 2, $H_{7,7'}$), 4.00 - 4.25 (m, 1, H_6), 4.20 - 4.40 (m, 1, H_3), 4.52 (s, 2, $\underline{CH_2}C_6H_5$), 4.60 - 4.68 (m, 2, H_4 and H_5), 5.25 (d, $\underline{J}_{2-3}$ = 4.5 Hz, 1, H_2), 5.90 - 6.40 (bd, 2, $CO\underline{NH_2}$), 7.31 (s, 5, C_6H_5).

3,6-Anhydro-2-O-acetyl-4,5-O-isopropylidene-D-glycero-D-(allo and altro)-heptonamide (95 and 96)

A solution of the 7-O-benzyl-α-acetyloxy amide (93 or 94) (4.0 g, 10.55 mmol) in 98% ethanol (100 ml) was hydrogenated over 5% Pd-C (2 g) at 60 psi. The reaction was monitored by TLC (ethyl acetate, starting material $R_f = 0.75$, product $R_f = 0.25$). After 8 h the mixture was filtered and evaporated to give 3.1 g (quantitative) of 95 or 96 homogeneous by TLC: MS m/e 290.1244 (3.5, M^+, calcd for $C_{12}H_{20}NO_7$: 290.1248), 275.0966 (13.99, $M^+ + 1 - CH_3$), 274.0933 (100, $M^+ - CH_3$), 232.0824 (24.25, $M^+ + 1 - CH_3 - COCH_3$).

3,6-Anhydro-2-O-acetyl-4,5-O-isopropylidene-7-O-methanesulfonyl-D-glycero-D-(allo and altro)-heptonamide (97 and 98)

A solution of the α-acetyloxy amide (95 or 96) (5.0 g, 17.3 mmol) in pyridine (30 ml) and CH_2Cl_2 (30 ml) at 0°C, was treated dropwise with methanesulfonyl chloride (4.0 g, 34 mmol) in methylene chloride (10 ml). The solution was left at 0°C for 8 h, diluted with methylene chloride and poured into ice water (25 ml). The organic phase was washed with saturated brine (3 x 10 ml), dried and evaporated. This residue was chromatographed on silica (50 gm, 3 x 20 cm), eluting with solvent B followed by ethyl acetate to give 5.6 g

(88%) of **97** or **98** as a white foam. An analytical sample of the faster migrating isomer (**97**) was crystallized from chloroform-ether. The slower isomer (**98**) was obtained as a white solid foam.

"Faster" isomer (**97**): mp 133 - 134°C; $[\alpha]_D^{23} - 11°$ (*c* 0.1, $CHCl_3$); IR (KBr), 1180 cm^{-1}, 1260 cm^{-1} (SO_2CH_3), 1750 cm^{-1} ($COCH_3$), 3400 cm^{-1} ($CONH_2$); NMR ($CDCl_3$) δ 1.35 and 1.54 (s+s, 3+3, $C(CH_3)_2$), 2.20 (s, 3, $COCH_3$), 3.06 (s, 3, SO_3CH_3), 4.10 - 4.40 (m, 4, H_3, H_6 and $H_{7,7'}$), 4.58 (d of d, J_{5-6} = 4.5 Hz, J_{4-5} = 6.5 Hz, 1, H_5), 4.93 (d of d, J_{4-5} = 6.5 Hz, J_{4-3} = 4 Hz, 1, H_4), 5.32 (d, J_{2-3} = 4 Hz, 1, H_2), 6.0 - 6.5 (bd, 2, $CONH_2$); MS m/e 368.1006 (1.04, M^++1, calcd for $C_{13}H_{22}NO_9S$: 368.1015), 352.0706 (100, M^+-15), 323.0791 (0.92, M^+ - $CONH_2$), 310.0604 (13.00, M^++1 - CH_3-$COCH_3$), 308.0809 (3.48, M^+-CH_3-$CONH_2$).

Anal. Calcd for $C_{13}H_{21}NO_9S$: C, 42.50; H, 5.72; N, 3.81; S, 8.72. Found: C, 42.54; H, 5.75; N, 3.92; S, 8.81.

"Slower" isomer: $[\alpha]_D^{23} + 14°$ (c 0.1, $CHCl_3$); NMR ($CDCl_3$) δ 1.35 and 1.54 (s+s, 3+3, $C(CH_3)_2$), 2.18 (s, 3, $COCH_3$), 3.04 (s, 3, SO_3CH_3), 4.10 - 4.70 (m, 6, sugar), 5.22 (d, J_{2-3} = 4 Hz, 1, H_2), 6.05 - 6.40 (bd, 2, $CONH_2$).

3,6-Anhydro-2-O-acetyl-7-deoxy-4,5-O-isopropylidene-D-glycero-D-(allo and altro)-heptonamide (101 and 102)

A solution of the 7-O-mesyl derivative (97 or 98) (5.0 g, 13.6 mmol) in 2-butanone (200 ml) was treated with sodium iodide (4.08 gm, 27.2 mmol) and stirred under nitrogen at reflux for 20 h, cooled and evaporated to a yellow paste. This residue was dissolved in ethyl acetate (200 ml) and 5% aqueous sodium bisulfite (25 ml). The organic phase was washed with saturated brine (25 ml), dried and evaporated to give 5.5 g (quantitative) of (99 or 100) as a colorless syrup: MS m/e 383.9952 (54.42, M^{+}+1-CH_3, calcd for $C_{11}H_{15}NO_6I$: 383.9946).

This syrup was dissolved in 98% ethanol (200 ml, treated with triethyl amine (5 ml) and a chip of dry ice, and hydrogenated over 5% Pd-C (2.5 g) at 20 psi in a Parr shaker. After 10 h the reaction was filtered through a celite pad and evaporated. The residue was dissolved in ethyl acetate (200 ml) and washed with saturated brine (25 ml) containing sodium bisulfite (500 mg). The aqueous phase was extracted with ethyl acetate (3 x 20 ml). The combined organic phase was dried, evaporated, and purified by chromatography on silica (50 g, 3 x 20 cm). Elution with solvent B, followed by ethyl acetate gave the desired product.

"Faster" isomer (**101**): The yield after chromatography was 3.5 g (94%) of **101**: $[\alpha]_D^{23}$ - 30° (*c* 0.1, $CHCl_3$): IR (film) 1690 cm^{-1} ($CONH_2$), 1750 cm^{-1} ($COCH_3$); NMR ($CDCl_3$) δ 1.27 (d, J_{7-6} = 6 Hz, 3, H_7), 1.36 and 1.56 (s+s, 3+3, $C(CH_3)_2$), 2.16 (s, 3, $COCH_3$), 3.98 (q, J_{7-6} = 6 Hz, J_{6-5} = 5 Hz, 1, H_6), 4.10 - 4.30 (m, J_{5-6} = 5 Hz, J_{5-4} = 6.5 Hz, J_{3-2} = 4 Hz, J_{3-4} = 3.5 Hz, 2, H_5 and H_3), 4.88 (d of d, J_{4-5} = 6.5 Hz, J_{4-3} = 3.5 Hz, 1, H_4), 5.28 (d, J_{2-3} = 4 Hz, 1, H_2), 6.3 - 6.6 (bs, 2H, $CONH_2$). MS m/e 274.1290 (1.24, M^++1, calcd for $C_{12}H_{20}NO_6$: 274.1292), 259.1015 (9.91, M^++1-CH_3), 258.0981 (79.74, M^+-CH_3), 216.0874 (5.77, M^++1-CH_3-$COCH_3$), 215.0787 (5.40, M^+-CH_3-$COCH_3$), 214.0720 (14.42, M^+-1-CH_3-$COCH_3$).

Anal. Calcd for $C_{12}H_{19}NO_6$: C, 52.75; H, 6.96; N, 5.13. Found: C, 52.37; H, 7.11; N, 4.80.

"Slower isomer (**102**). The yield after chromatography was 3.4 g (91%) of **102**: $[\alpha]_D^{23}$- 5° (*c* 0.1, $CHCl_3$); NMR ($CDCl_3$) δ 1.33 (d, J_{7-6} = 6 Hz, 3, CH_3), 1.36 and 1.56 (s+s, 3+3, $C(CH_3)_3$), 2.20 (s, 3, $COCH_3$), 4.00 (q, J_{6-7} = 6 Hz, J_{6-5} = 5 Hz, 1, H_6), 4.15 - 4.35 (m, 2, H_3 and H_5), 4.64 (d of d, J_{4-5} = 6 Hz, J_{4-3} = 3 Hz, 1, H_4), 5.25 (d, J_{2-3} = 4 Hz, 1, H_2), 6.1 - 6.5 (bs, 2H, $CONH_2$).

3,6-Anhydro-7-deoxy-4,5-*O*-isopropylidene-*D*-glycero-*D*-(allo and altro)-heptonamide (103 and 104)

A solution of the α-acetyloxy amide (101 or 102) (4.0 g, 14.6 mmol) in methanol (100 ml) was treated with saturated methanolic ammonia (100 ml), left at 0°C for 16 h, and then evaporated to give 3.4 g (quantitative) of a white solid, homogeneous by TLC (EtOAc, starting material R_f = 0.5, product; faster isomer R_f = 0.26, slower isomer R_f = 0.24).

"Faster" isomer (103): The solid was crystallized from methanol-ether-Skelly "B" to give 2.95 g (87%) of 103: mp 174 - 175°C; $[\alpha]_D^{23}$ - 10° (*c* 0.1, $CHCl_3$); IR (KBr) 1650 cm^{-1} ($\underline{CO}NH_2$), 3300 - 3400 ($CO\underline{NH}_2$, OH); NMR (DMSO-d_6) δ 1.19 (d, J_{7-6} = 7 Hz, 3, H_7), 1.22 and 1.41 (s+s, 3+3, $C(CH_3)_2$), 3.7 - 4.8 (m, 5, sugar), 5.7 (d, 1, OH), δ ~7.25 (bs, 2, $CONH_2$); Ms m/e 232.1186 (1.88, M^++1, calcd for $C_{10}H_{18}NO_5$: 232.1185), 231.1111 (0.75, M^+), 217.0908 (8.87, M^++1-CH_3), 216.0874 (84.21, M^+-CH_3), 188.1009 (2.49, M^++1-$CONH_2$), 187.0978 (23.06, M^+-$CONH_2$), 174.0760 (6.32, M^++1-$CONH_2$-CH_3), 174.0691 (20.91, M^++1-$CONH_2$-CH_3), 157.0861 (100, M^+-$C_2H_4NO_2$).

Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.95; H, 7.36; N, 6.06. Found: C, 51.49; H, 7.26; N, 5.71.

"Slower" isomer (104): The solid was crystallized from chloroform-ether-Skelly "B" to give 2.76 g (82%)

of 104: mp 102 - 103°C; $[\alpha]_D^{23}$ - 15° (c 0.1, $CHCl_3$); NMR ($DMSO-d_6$) δ 1.16 (d, J_{7-6} ≈ 7 Hz, 3, H_7), 1.24 and 1.42 (s+s, 3+3, $C(CH_3)_2$), 3.7 - 4.8 (m, 5, sugar) 5.5 (d, 1, OH), δ ~7.15 (bs, 2, $CONH_2$).

Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.95; H, 7.36; N, 6.06. Found: C, 51.90; H, 7.63; N, 5.99.

3,6-Anhydro-7-deoxy-4,5-O-isopropylidene-2-O-methanesulfonyl-D-glycero-D-(allo and altro)-heptonamide (105 and 106)

A solution of the α-hydroxy amide (103 or 104) (2.31 g, 10 mmol) in pyridine (25 ml) and methylene chloride (10 ml) at 0°C was treated dropwise with methanesulfonyl chloride (5.7 g, 50 mmol) in methylene chloride (10 ml). After 4 h at 0°C the solution was treated with a chip of ice, diluted with ethyl acetate (150 ml), washed with saturated brine (3 x 10 ml), dried and evaporated to a syrup. This residue was chromatographed on silica (50 g, 3 x 20 cm), eluting with solvent A followed by ethyl acetate to give 2.6 g (84%) of (105 or 106).

"Faster" isomer (105): The residue was crystallized from ether-Skelly "B" to give 2.15 g (69%) of crystalline 105: mp 104 - 105°C; $[\alpha]_D^{23}$ + 9 (c 0.1, $CHCl_3$), IR (KBr) 1630 cm^{-1} ($CONH_2$); NMR ($CDCl_3$) δ 1.32 (d, J_{7-6} = 6 Hz, 3, H_7), 1.36 and 1.52 (s+s, 3+3, $C(CH_3)_2$), 3.15 (s, 3, SO_3CH_3), 4.00 (q, J_{6-7} =

$\underline{J}_{6-5} \simeq 6$ Hz, 1, H_6), 4.15 - 4.95 (m, 2, H_3 and H_5), 4.81 (d of d, $\underline{J}_{4-5} = 6.5$ Hz, $\underline{J}_{4-3} = 4$ Hz, 1, H_4), 5.13 (d, $\underline{J}_{2-3} = 3.5$ Hz, 1, H_2), 6.25 and 6.7 (bs, 2, $CONH_2$); MS m/e 295.0677 (10.27, M^++1-CH_3, calcd for $C_{10}H_{17}NO_7S$: 296.0716), 294.0651 (83.65, M^+-CH_3), 157.0860 (16.37, M^+-$C_3H_6NO_4S$).

Anal. Calcd for $C_{11}H_{19}NO_7S$: C, 42.72; H, 6.15; N, 4.53; S, 10.36. Found: C, 42.60; H, 6.08; N, 4.27; S, 10.25.

"Slower" isomer (106): The product was crystallized as above to give 2.4 g (92%) of 106: mp 143 - 144°C; $[\alpha]_D^{23}$-35° ($\underline{c}$ 0.1, $CHCl_3$); NMR ($CDCl_3$) δ 1.32 (d, $\underline{J}_{7-6}$ = 6 Hz, 3, H_7), 1.36 and 1.52 (s+s, 3+3, $C(CH_3)_2$), 3.17 (s, 3, SO_3CH_3), 4.02 (m, $\underline{J}_{6-7} \simeq \underline{J}_{6-5} \simeq 6$ Hz, 1, H_6), 4.20 - 4.35 (m, 2, H_3 and H_5), 4.80 (d of d, $\underline{J}_{4-5} = 6.5$ Hz, $\underline{J}_{4-3} = 4$ Hz, 1, H_4), 5.00 (d, $\underline{J}_{2-3} = 4$ Hz, 1, H_2), 6.25 and 6.7 (bs, 2, $CONH_2$).

3,6-Anhydro-2-azido-2,7-dideoxy-4,5-O-isopropylidene-D-glycero-D-(allo and altro)-heptonamide (107 and 108).

A solution of the α-mesylate amide (105 or 106) (2.31 g, 7.5 mmol) in dimethylformamide was treated with lithium azide (1.85 g, 38 mmol) and stirred at 80°C for 5 h. The mixture was concentrated to a yellow paste, dissolved in ethyl acetate (100 ml) washed with saturated brine (3 x 10 ml), dried and evaporated. The residue was chromatographed on silica (25 g, 2.2 x 18 cm), eluting with solvent B followed by ethyl acetate to give the desired product.

"Faster" isomer (107): The yield after chromatography was 1.77 g (93%) of solid 107. An analytical sample of 107 was crystallized from ether-Skelly "B": mp 126 - 127°C; $[\alpha]_D^{23}$ - 32° (c 0.1, $CHCl_3$), IR (KBr) 1600 cm^{-1} (CONH_2), 2120 cm^{-1} (N_3), 3300 - 3400 (CONH$_2$); NMR ($CDCl_3$) δ 1.31 (d, $\underline{J}_{7-6}$ = 6.5, 3, H_7), 1.34 and 1.52 (s+s, 3+3, $C(CH_3)_2$), 4.00 (q, $\underline{J}_{6-7}$ = $\underline{J}_{6-5}$ = 6.5 Hz, 1, H_6), 4.26 (d, $\underline{J}_{2-3}$ = 4Hz, 1, H_2), 4.27 (t, $\underline{J}_{5-6}$ = $\underline{J}_{5-4}$ = 6.5 Hz, 1, H_5), 4.42 (t, $\underline{J}_{3-2}$ = $\underline{J}_{3-4}$ = 4 Hz, 1, H_3), 4.60 (d of d, $\underline{J}_{4-5}$ = 6.5 Hz, $\underline{J}_{4-3}$ = 4 Hz, 1, H_4); MS m/e 241.0934 (64.41, M^+-CH_3, calcd for $C_9H_{13}N_4O_4$: 241.0937), 214.1081 (48.10, M^+-N_3), 199.0836 (1.23, M^+-N_3-CH_3), 157.0863 (93.99, M^+-$C_2H_3N_4O$).

Anal. Calcd for $C_{10}H_{16}N_4O_4$: C, 46.87; H, 6.25; N, 21.88. Found C, 46.59; H, 6.50; N, 22.06.

"Slower" isomer (108): The slower migrating isomer was crystallized from ether to give 1.8 g (94%) of 108: mp 114 - 116°C. An analytical sample was recrystallized from ether: mp 119 - 120°C; $[\alpha]_D^{23}$ - 84° (c 0.1, $CHCl_3$); NMR ($CDCl_3$) δ 1.36 (d, $\underline{J}_{7-6}$ = 6.5 Hz, 3, H_7), 1.34 and 1.51 (s+s, 3+3, $C(CH_3)_2$), 3.90 - 4.90 (m, 4, H_2, H_3, H_5 and H_6), 4.79 (d of d, $\underline{J}_{4-5}$ = 6.5 Hz, $\underline{J}_{4-3}$ = 3 Hz, 1, H_4), 6.0 and 6.4 (bs, s, $CONH_2$).

Anal. Calcd for $C_{10}H_{16}N_4O_4$: C, 46.87; H, 6.25; N, 21.88. Found: C, 47.23; H, 6.55; N, 21.50.

Methyl 3,6-anhydro-2-azido-2,7-dideoxy-D-glycero-D (allo and altro)-heptonoate (109 and 110)

A solution of the α-azido amide (107 or 108) (1.5 g, 5.8 mmol) in methanol (50 ml, dry and distilled) was stirred at reflux with ANGC(H^+) resin (5 g). After 4.5 h an additional portion of resin (5 g) was added to the refluxing mixture. After a total reflux time of 9 h the mixture was filtered using a celite pad, evaporated, and chromatographed over silica (20 g, 2.3 x 12 cm). Elution with solvent B followed by ethyl acetate gave 1.15 g (85%) of 109 or 110 as a stiff syrup.

"Faster" isomer (109): $[\alpha]_D^{23}$ - 62° (c 0.1, $CHCl_3$); IR (film) 1740 cm^{-1} (CO_2CH_3), 2120 cm^{-1} (N_3); NMR ($CDCl_3$) δ 1.31 (d, J_{7-6} = 6 Hz, 3, H_7), 3.5 - 4.4 (m, 7, sugar, OH), 3.84 (s, 3, CO_2CH_3); MS m/e 213.0749 (2.38, M^+-H_2O, calcd for $C_8H_{11}N_3O_4$: 213.0749), 117.0549 (98.44, $M^+-C_3H_4N_3O_2$).

Anal. Calcd for $C_8H_{13}N_3O_5$: C, 41.56; H, 5.63; N, 18.18. Found: C, 41.08; H, 5.72; N, 18.08.

"Slower" isomer (110): $[\alpha]_D^{23}$ + 4° (c 0.1, $CHCl_3$); NMR ($CDCl_3$) δ 1.31 (d, J_{7-6} = 6 Hz, 3, H_7), 3.5 - 4.4 (m, 7, sugar and OH), 3.82 (s, 3, CO_2CH_3).

Methyl 3,6-anhydro-2-azido-2,7-dideoxy-2,3-*O*-thiocarbonato-*D*-glycero-*D*-(altro and allo)-heptonoate (**111** and **112**).

A solution of the α-azido ester (**109** or **110**) (1.15 g, 5 mmol) in acetone (50 ml) was treated with diimidazole thiocarbonate (1.78 g, 20 mmol) and stirred at room temperature. After 12 h TLC (EtOAc/Skelly "B" 1:1, starting material R_f = 0.5, product R_f = 0.70) revealed the reaction was complete. The solvent was evaporated, the residue dissolved in ethyl acetate (100 ml) and washed with 1*N* hydrochloric acid (2 x 10 ml), saturated brine (3 x 20 ml), dried and evaporated. This residue was dissolved in ether (50 ml) and rapidly filtered through silica (5 g). The silica was washed with ether (20 ml) and the combined ether solutions were evaporated to give 1.25 g (92%) of **111** or **112**. The faster moving isomer was isolated as a solid. The slower migrating isomer was recovered as a stiff syrup.

"Faster isomer" (**111**): A sample was crystallized from ether-Skelly "B"; mp 95 - 96°C; IR (FT) (KBr) 1750 cm^{-1} (CO_2Me), 2120 cm^{-1} (N_3); UV (MeOH) max 238 nm NMR ($CDCl_3$) δ 1.43 (d, J_{7-6} = 6 Hz, 3, H_7), 3.84 (s, 3, CO_2CH_3), 4.07 (d, J_{2-3} ≃ 3.5 Hz, 1, H_2), 4.13 (m, J_{6-7} ≃ J_{6-5} ≃ 6 Hz, 1, H_6), 4.55 (t, J_{3-4} = 3.0 Hz, J_{3-2} ≃ 3.5 Hz, 1, H_3), 4.85 (d of d, J_{5-4} = 8 Hz, J_{5-6} = 6.0 Hz, 1, H_5), 5.32 (d of d, J_{4-5} = 8 Hz,

$\underline{J}_{4-3}$ = 3.0 Hz, H_4); MS m/e 273.0420 (100, M^+, calcd for $C_9H_{11}N_3O_5S$: 273.0420), 159.0155 (13.40, f), 127.0397 (20.07, g), 83.0494 (26.53, c).

"Slower" isomer (112): this isomer was isolated as a viscous syrup: IR (Nujol) 2120 cm^{-1} (N_3), 1745 cm^{-1} (CO_2CH_3); UV (MeOH) 238 nm; NMR ($CDCl_3$) δ 1.44 (d, $\underline{J}_{7-6}$ = 6 Hz, 3, H_7), 3.84 (s, 3, CO_2CH_3), 4.14 (q, $\underline{J}_{6-7} \approx \underline{J}_{6-5} \approx$ 6 Hz, 1, H_6), 4.38 (d, $\underline{J}_{2-3} \approx$ 3.5 Hz, 1, H_2), 4.51 (t, $\underline{J}_{3-4}$ = 3.0 Hz, $\underline{J}_{3-2} \approx$ 3.5 Hz, 1, H_3), 4.82 (d of d, $\underline{J}_{3-4}$ = 8 Hz, $\underline{J}_{5-6}$ = 6.0 Hz, 1, H_5), 5.34 (d of d, $\underline{J}_{4-5}$ = 8 Hz, $\underline{J}_{4-3}$ = 3.0 Hz, 1, H_4); MS m/e 273.0422 (100, M^+, calcd for $C_9H_{11}N_3O_5S$: 273.0402), 159.0115 (19.10, f), 127.0397 (8.33, g), 83.0497 (25.41, c).

2-(R and S)-amino-2-[2,5-dihydro-5(R)-methylfuran-2(R)-yl]ethanoic acid (113 and 114)

A solution of the thiocarbonate sugar (111 or 112) (273 mg, 1 mmol) in trimethylphosphite (25 ml) was stirred at reflux for 14 h under nitrogen, cooled and evaporated to a syrup. This residue was saponified with aqueous 1N sodium hydroxide (20 ml) at 90°C for 0.5 h, cooled to 0°C and acidified to pH = 2 with aqueous 1N hydrochloric acid. This solution was applied to a column of ANGC(H^+) resin (20 g) and the column was washed with 0.1N hydrochloric acid (100 ml) followed by water (200 ml). The product was eluted with 0.5*N* ammonium hydroxide and the ninhydrin positive fractions were collected and evaporated to give 50 mg (32%) of **114** or **113** as a tan colored solid. By allowing a solution of **114** in acetonitrile-methanol to slowly evaporate, this product was obtained as a white microcrystalline solid: mp 175 - 178°C (d); $[\alpha]_D^{23}$ = -50° (*c* .1, H_2O), $[\alpha]_D^{23}$ = -8° (*c* .1, 1*N* HCl), IR (Nujol) 3000 cm^{-1} (NH_3^+), 1630 cm^{-1} (CO_2), 1590 cm^{-1}, 1460 cm^{-1} and 1380 cm^{-1}; C.D. (*c* 1 mg/ml, 1*N* HCl and 6*N* HCl), $[\theta]_{216}$ = +2,200; ORD (*c* ~1 mg/ml, 6*N* HCl), $[\phi]_{210}$ = 1,100: NMR (100 MHz) (D_2O) δ 1.38 (d, J_{7-6} = 6.5 Hz, 3, H_7), 3.93 (d, J_{2-3} = 3 Hz, 1, H_2), 5.02 (m, 1, H_6), 5.34 (m, 1, H_3), 5.92 and 6.20 (ABX, J_{4-5} = 6 Hz, J_{4-3} = 2 Hz, J_{5-6} = 1.5 Hz, 2, $H_{4,5}$); NMR (200 MHz) (D_2O) δ 1.34 (d, J_{7-6} = 6.5 Hz, 3, H_7), 3.81 (d, J_{2-3} = 3 Hz, 1, H_2), 4.95 (m, J_{6-7} = 6.5 Hz, J_{6-5} = 2 Hz, J_{6-4} = 0.5 Hz, J_{6-3} = 4.5 Hz, J_{6-7} ≃ 0 Hz, 1, H_6), 5.24 (m, J_{3-2} = 3.0 Hz, J_{3-4} = 2.5 Hz, J_{3-5} = 1 Hz, J_{3-6} = 4.5 Hz, 1, H_3), 5.82 and 6.10 (ABX, J_{4-5} = 6 Hz, J_{4-3} = 2.5 Hz, J_{5-6} = 2 Hz, 2, H_4 and H_5); NMR (400 MHz) (D_2O) δ 1.34 (d, J_{7-6} = 6.5 Hz, 3, H_7), 3.88 (d, J_{2-3} = 3 Hz, 1, H_2), 5.01 (m, 1, H_6), 5.31 (m, 1, H_3), 5.87 and 6.15 (d, 2, H_4 and H_5; ^{13}C NMR (D_2O) (ppm from Me_4Si) 21.2 (CH_3), 57.4 (C_2), 83.6 and 84.6 (C_3,C_6), 125.1 and 136.0 (C_4,C_5)

and 172.0 (CO_2H).

The α-amino diastereomer 113 was recovered as a tan colored solid: mp 185 - 190°C; $[\alpha]_D^{23}$ = +21° (c .1, 1N HCl: optical rotation calculated for a mixture of 113 (82%) and 114 (18%), [+35° (119, Joullié) x 0.82 ≈ 28°] + [-8° (114, this work) x 0.18 ≈ -1] = +27°; CD (c ~1 mg/ml, 1N HCl) [θ] = +1700; NMR (100 MHz, D_2O) δ 1.38 (d, J_{7-6} = 6.5 Hz, 3, H_7), 4.06 (d, J_{2-3} = 4 Hz, 1, H_2), 5.06 (m, 1, H_6), 5.36 (m, 1, H_3), 5.77 and 6.18 (ABX, J_{4-5} = 7 Hz, J_{5-6} = 2 Hz, J_{4-3} = 1.5 Hz), NMR (200 MHz, D_2O) δ 1.28 (d, J_{7-6} = 7 Hz, 3, H_7), 3.99 (d, J_{2-3} = 4 Hz, 1, H_2), 5.00 (m, J_{6-7} = 7 Hz, J_{6-5} = 2.5 Hz, J_{6-4} = 1 Hz, J_{6-3} = 4.5 Hz, J_{6-2} ≈ 0 Hz, 1, H_6), 5.30 (m, J_{3-2} = 4 Hz, J_{3-4} = 3 Hz, J_{3-5} = 1 Hz, J_{3-6} = 4.5 Hz, 1, H_3), 5.70 and 6.12 (ABX, J_{4-5} = 6.5 Hz, J_{4-3} = 3 Hz, J_{5-6} = 2.5 Hz, 2, H_4, H_5), NMR (400 MHz, D_2O) δ 1.31 (d, J_{7-6} = 6.5 Hz, 3, H_7), 4.06 (d, J_{2-3} = Hz, 1, H_2), 5.02 (m, 1, H_6), 5.32 (m, 1, H_3), 5.72 (d, 1, H_5), 6.14 (d, 1, H_4), ^{13}C NMR (D_2O) ppm 20.9 (C_7), 56.9 (C_2), 84.0 and 83.6 (C_3 and C_4), 122.9 and 136.3 (C_4 and C_5).

2(S)-Amino-2-[tetrahydro-5(R)-methylfuran-2(R)-yl]-ethanoic acid (115).

A solution of our synthetic cis product (114) (5 mg, 0.03 mmol) in water (5 ml) was hydrogenated over 5% Pd-C (5 mg) at atmospheric pressure for 10 h, filtered through celite and evaporated to give 115 (5 mg) as a solid; CD ($\underline{c}$ ≃ 2 mg/ml, 6$\underline{N}$ HCl) $[\theta]_{215}$ = +2,000; NMR (200 MHz) (D_2O) δ 1.22 (d, 3, H_7), 1.40 - 2.20 (m, 2, $H_{4,5}$) 3.65 (d, 1, H_2), 3.70 - 4.50 (m, 2, $H_{3,6}$).

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